



Royal College  
of Nursing

# Assessing, managing and monitoring biologic therapies for inflammatory arthritis

*Guidance for rheumatology  
practitioners*

*An advisory document prepared by the Royal  
College of Nursing Rheumatology Biologics  
Working Party, in conjunction with other members  
of the Arthritis Musculoskeletal Alliance.*

*This publication is supported by the  
pharmaceutical industry.*



Royal College  
of Nursing

# Assessing, managing and monitoring biologic therapies for inflammatory arthritis

## *Guidance for rheumatology practitioners*

An advisory document prepared by the Royal College of Nursing Rheumatology Biologics Working Party, in conjunction with other members of the Arthritis Musculoskeletal Alliance.

Sponsorship was received from the following pharmaceutical companies:



 A member of the Roche group



The monies received were used in the development, publication and distribution of this guidance by the RCN. The sponsoring companies had no editorial control over or input into this guidance except to review the guidance for factual accuracy. The views and opinions contained in this guidance are those of the authors and not necessarily those of the sponsoring companies.

# Contents

Introduction	2	<b>Part 2: Children and young people</b>	
Core documents	3	Introduction	34
<b>Part 1: Adult patients</b>	5	<b>Section 1: Assessing and managing children and young people needing biologic therapies</b>	35
<b>Section 1: Assessing and managing patients</b>	5	Special needs of children and young people	35
Eligibility	5	The Biologics Register	36
Selecting patients for treatment	6	Special skills for working with children and young people receiving biologic therapies	36
Disease-specific assessment and management	7	Assessing and managing patients	36
1. Rheumatoid arthritis: assessment of patients before and during treatment	7	1. Selecting patients for treatment	36
2. Ankylosing spondylitis: assessment of patients before and during treatment	8	2. Detailed assessment of patients	37
3. Psoriatic arthritis: assessment of patients before and during treatment	9	3. Before subcutaneous biologic therapies are administered	38
Screening and risks	10	4. Drug dosages	38
1. Pre-treatment screening and monitoring	10	5. Follow-up care between treatments	38
2. Specific screening and monitoring issues	10	<b>Section 2: Resource planning for children and young people</b>	39
3. Blood monitoring while on treatment	12	1. Biologics Register	39
4. Risk of infection: General areas for caution	12	2. Providing a seamless service	39
5. Risk of infection: Tuberculosis	14	3. Tailoring support from pharmaceutical companies	40
6. Immunisation	15	4. Specialist expertise and skill-mix	40
7. Cardiac function	17	<b>Appendices</b>	41
8. Neurological issues	17	1. Patient management workbook	41
9. Surgery	17	• Section 1: disease specific eligibility criteria	41
10. Malignancy	18	• Section 2: exclusion criteria	42
11. Skin	18	• Section 3: screening prior to treatment	43
12. Pregnancy and breastfeeding	19	• Section 4: general and infection screening	44
13. Other potential side effects	19	2. Flow algorithm for patients receiving intravenous biologic therapy	45
14. Treatment-related reactions	20	3. British Society for Rheumatology Biologics Register (BSRBR)	46
15. Limitation and areas of research/debate when assessing treatment benefit	20	4. Training patients to self administer subcutaneous biologic therapies: A framework for registered rheumatology nurses	47
<b>Section 2: Managing intravenous and subcutaneous biologic therapies</b>	22	5. Detailed guidance for screening and managing tuberculosis (TB)	55
Preparing to administer intravenous and subcutaneous therapies	22	6. Euler response criteria	57
Conditions for administration	22	7. Business planning and resources	58
Administration and management of intravenous biologic therapies	23	8. Classification of juvenile idiopathic arthritis (JIA)	60
1. Abatacept	23	9. BSPAR guidelines for prescribing biologic therapies in children and young people with JIA	61
2. Infliximab	25	10. Testing for varicella antibodies in children	63
3. Rituximab	27	11. The RCN Rheumatology Working Parties	64
4. Tocilizumab	29	12. Grading of evidence chart	66
Administration and management of subcutaneous biologic therapies	30	13. Websites and resources	67
Therapies delivered subcutaneously	30	<b>References</b>	69
Delivery of subcutaneous therapies to patients' homes	32	Part 1: Adult patients	69
Ongoing management for all biologic therapies	32	Part 2: Children and young people	72
		Further reading	73

# Introduction

## Biologic therapies

This document provides practitioners with information to help them care for patients with different forms of inflammatory arthritis, in all care settings. Its focus is to ensure that practitioners have knowledge of the assessment, screening and management of patients with all forms of inflammatory arthritis when these patients are being considered for the new therapies sometimes referred to as 'biologics'.

The role of biologic therapies in the treatment and management of patients with inflammatory joint disease is an evolving area that has significant implications for all practitioners. The term 'biologic' describes treatments developed and produced in live cell systems (biologically active systems). In biologics for inflammatory arthritis, the body's antibodies or proteins were initially developed to target or disable specific pro-inflammatory cytokines. The first biologic therapies to be developed targeted the pro-inflammatory cytokines tumour necrosis factor alpha (anti-TNF $\alpha$ ) and interleukin 1 (IL-1receptor agonist).

To date, almost 1.5 million patients have been treated worldwide with anti-tumour necrosis factor alpha (known as anti-TNF $\alpha$ , anti-TNFs or TNF inhibitors). The resultant large volume of research into anti-TNF $\alpha$  therapies initially showed evidence of the safety and efficacy of these therapies for treating rheumatoid arthritis (RA), but more recently also for other conditions, such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Research has also identified benefits including the identification of new therapeutic targets along the immunological pathway, and highlighted the potential benefits of biologic therapies in treating other long-term conditions.

There are a number of biologic therapies for different indications used in the field of rheumatology. This document covers a number of those licensed (or pending license) for inflammatory joints diseases. These include:

- ◆ abatacept
- ◆ adalimumab
- ◆ certolizumab pegol

- ◆ etanercept
- ◆ golimumab
- ◆ infliximab
- ◆ rituximab
- ◆ tocilizumab (licensed January 2009).

## Providing updated guidance

Most rheumatology and specialist paediatric rheumatology units are already administering some (but not all) of these biologic therapies. The Royal College of Nursing (RCN) Rheumatology Forum Steering Committee, in consultation with clinicians, health care professionals and patient organisations, recognised the need to update the RCN's 2003 guidance in line with recent developments. Additional documents to support this document will be posted on the RCN Rheumatology Forum website as they become available ([www.rcn.org.uk/rheumatology](http://www.rcn.org.uk/rheumatology)).

The RCN set up a Rheumatology Biologics Working Party to update the original guidance. The working party was supported by Professor DGI Scott (who chaired the original group) and Dr Christopher Deighton, chair of the British Society of Rheumatology (BSR) Clinical Affairs Committee, Clinical Advisor to the current NICE RA Management guidelines and lead author of the updated BSR RA Biologics guidelines (pending publication). The support provided by both Professor Scott and Dr Deighton has been invaluable in developing this guidance (for full details of the working party membership, see Appendix 11).

The working party reviewed and considered five key areas:

- ◆ the evidence of licensed biologics, including changes to disease indications and achieving expert consensus on emerging evidence
- ◆ new treatments licensed or pending a license
- ◆ provision of guidance on specific clinical issues in assessing and managing patients receiving biologic therapies
- ◆ data collection requirements for current treatments, including the data for the British Society for Rheumatology Biologics Register (Appendix 3)
- ◆ practical and nursing resource implications for biologic therapies.

The evidence used to inform the development of this guidance document was chiefly derived as a result of drawing together a number of guideline documents. Where evidence was limited, the Working Party reviewed data and came to a consensus. Evidence was graded according to concise guidelines with randomised controlled trials of high quality and power being graded as the highest and categorised as Grade A evidence through to expert committee reports, opinions graded as category C (for grading, refer to the Royal College of Physicians website [www.rcplondon.ac.uk/clinical-standards](http://www.rcplondon.ac.uk/clinical-standards)) and Appendix 12.

## This document

This updated guidance document will help practitioners in the UK develop a standardised approach to caring for patients receiving biologic therapies. An extensive reference section includes core publications that we recommend you consult alongside this guidance.

The new guidance provides evidence and background reading, with notes on business and resource planning (Appendix 7), together with a practitioner's workbook to aid standardised assessment and management processes.

We cannot over emphasise the importance of collecting data for the BSR Biologics Register (BSRBR), as well as the data required according to your local NHS trust and departmental needs. To clarify what data is required for the BSRBR, please refer to the website for the most up to date information ([www.medicine.manchester.ac.uk](http://www.medicine.manchester.ac.uk)) and to Appendix 3. The BSRBR had registered (at 18 January 2009):

- ◆ 4850 infliximab
- ◆ 5306 etanercept
- ◆ 4700 adalimumab
- ◆ 149 anakinra
- ◆ 177 rituximab.

## Children and young people

As specialist practitioners, it is very important for you to be aware that children and young people require specific treatment which differs from the care of adults. Even though children or young people may currently be admitted to adult wards (although in line with the

Children's National Service Framework for England each trust should identify alternative locations to ensure children and young people receive care and treatment in specifically designated facilities), their clinical care should be managed according to paediatric rheumatology criteria for disease classification and treatment. Whatever the setting, you should seek guidance from a paediatric rheumatology consultant (Baildman, Davidson, 2008). Part 2 of this document covers specific issues for the care of children and young people, and has its own references section. Appendices 8, 9 and 10 refer specifically to paediatric care.

### The RCN Rheumatology Biologics Working Party

*Review date for this document: April 2012*

## Core documents

The first edition of this guidance document was published in 2003. Since then there have been a number of changes including new publications or updated guidance from professional organisations. It is vital that practitioners using this guidance document also refer to the core documents outlined below.

New publications or updated guidance from the professional organisations issued since 2003 include:

- ◆ NICE RA Management Guidelines (February, 2009)
- ◆ BSR update on guidance for anti-TNF $\alpha$  and eligibility criteria for patient with RA (2005, 2006)
- ◆ Scottish Intercollegiate Guidelines Early Management of RA (2000)
- ◆ BSR Guidelines for the management of RA (the first two years, 2006)
- ◆ BSR Guidelines for the management of RA (after the first two years, pending publication 2009)
- ◆ BSR Guidelines for the monitoring of disease modifying anti-rheumatic drugs (Chakravarety, 2008)
- ◆ BSR RA Biologics Guidance (pending publication 2009)
- ◆ BSR Guidance for treatment of AS with anti-TNF $\alpha$  (Keat *et al.*, 2005)
- ◆ BSR Guidance for the treatment of PsA with anti-TNF $\alpha$  (Kyle *et al.*, 2005)
- ◆ BSR Vaccinations in the immunocompromised person. Guidelines for the patient taking immunosuppressant, steroids and the new biologic therapies (2002)

- ◆ BTS recommendations for assessing risk and managing tuberculosis in people due to start anti-TNF $\alpha$  treatments (2005) ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk))
- ◆ The American College of Rheumatology Recommendations for the use of non biologic and biologic disease modifying anti-rheumatic drugs in RA (Saag *et al.*, 2008)
- ◆ The British Paediatric Rheumatology Group (2000). Guidelines for prescribing biologic therapies in children and young people with JIA. Guidance incorporated into 2002 NICE guidance for JIA (BPRG, 2000) ([www.bspar.org.uk](http://www.bspar.org.uk))
- ◆ BSR guidelines can be accessed at: [www.rheumatology.org.uk](http://www.rheumatology.org.uk)
- ◆ The National Patient Safety Agency for guidelines on the administration and management of injectable products. [www.npsa.nhs.uk](http://www.npsa.nhs.uk)
- ◆ Guidelines for the administration of medicines (NMC, 2004).

Also refer to local NHS trust policies.

## Core documents produced by the national regulatory bodies

The National Institute of Health and Clinical Excellence (NICE) is the National Health Service (NHS) regulatory body for England and Wales. It reviews research evidence and undertakes economic modelling to provide guidance to the Department of Health on the benefit of specific treatments.

In **Northern Ireland**, the Department of Health, Social Services and Public Safety (DHSSPS) has a formal link with NICE under which all NICE guidance documents published from 1 July 2006 are reviewed locally for their application to Northern Ireland. Guidance documents found to be applicable are endorsed by the DHSSPS for implementation. Arrangements have been put in place for health care professionals intending to undertake new interventional procedures to take into account NICE guidance.

In **Scotland**, there is some recognition of the NICE documents. However, the Scottish Intercollegiate Guidance Network (SIGN) provides a similarly regulatory function, providing guidance to Scottish Parliament on the benefit of specific treatments (see [www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk)). Patients receiving biologics in Scotland are also included in the BSRBR as for the rest of the UK.

Treatment criteria for biologic therapy have been outlined by NICE for England and Wales and The Scottish Consensus Guidelines (SCG) for Scotland.

Guidance documents:

- ◆ Ankylosing Spondylitis
  - TA143 adalimumab, etanercept, infliximab (2008)
- ◆ Psoriatic Arthritis
  - TA104 etanercept and infliximab (2006)
  - TA125 (moderate to severe) adalimumab (2007)
  - Review pending adalimumab, etanercept, infliximab (publication date 2010)
- ◆ Rheumatoid Arthritis NICE Technology Appraisal
  - TA72 anakinra guidance (2003)
  - TA125 RA (refractory) – rituximab (2007)
  - TA141 abatacept (2008)
  - TA130 adalimumab, etanercept and infliximab (2007)

Access to guidance documents: [www.nice.org.uk](http://www.nice.org.uk).

NICE and SIGN require adherence by health care practitioners to their guidance and recommend local and national audits. NHS funders of drug budgets may consider medical exception reports to request treatment for patients who fail to fulfil the treatment criteria but are deemed to have specific clinical need ([www.nice.org.uk](http://www.nice.org.uk) or [www.sign.ac.uk](http://www.sign.ac.uk)).

Other core documents include:

- ◆ Summary of Product Characteristics (SPC) of each of the therapies discussed. SPCs provide comprehensive information about the specific biologic therapy, and can be accessed at: [www.medicines.org.uk](http://www.medicines.org.uk)
- ◆ The Department of Health Green Book (2006) Department of Health, London: The Stationery Office.
- ◆ Arthritis Research Campaign ([www.arc.org.uk](http://www.arc.org.uk)) and Skills for Health competency frameworks ([www.skillsforhealth.org.uk](http://www.skillsforhealth.org.uk)).

# 1 Adult patients

The aim of this guidance document is to provide practitioners with an outline of biologic therapies (licensed or pending license) and refer the reader to additional key documents. Unless otherwise specified the guidance refers to all therapies, although the bulk of evidence relates to research and observational data collected for national registries in managing patients treated with anti-TNF $\alpha$  therapies.

**Note:** Co-prescribing of more than one biologic agent is contraindicated for all therapies outlined in this document. Co-prescription of a disease modifying anti-rheumatic drug (such as methotrexate (MTX)) with a biologic agent is commonly licensed for RA and has frequently been shown to potentiate the action of biologic agents.

## Section 1: Assessing and managing patients

### Eligibility for treatment

The BSR recognises that although recently published NICE guidance for RA continues to stipulate the original eligibility criteria for anti-TNF $\alpha$  therapies, further evidence will be reviewed by BSR Standards and the Audit Guideline group to evaluate the most effective method of assessing eligibility and treatment response for future use (BSR, pending publication).

As the research evidence increases and treatment criteria are set, it is possible to estimate the number of RA patients who are eligible for anti-TNF $\alpha$  therapies. For other conditions, however, current NICE appraisal technologies statistics do not give us such a clear picture of eligible populations.

- ◆ RA: approximately 40-50 patients per 100,000 of the population. Of the 400,000 people with RA in England and Wales, approximately 15% will have severe disease with the potential to warrant biologic therapies if disease modifying drug therapies fail to control the disease.
- ◆ AS: the prevalence of clinically significant AS is estimated to be 0.15% using Finnish data from mid 2004. Further research is needed to identify in more detail the proportion of patients who would gain

significant benefit from biologic therapies.

- ◆ PsA: the definitive diagnosis of PsA remains an area of discussion and further refinement. Although there is limited evidence on severity and prevalence, it is said to be in the region of 0.15-1%. The estimated number of those diagnosed with PsA and eligible for biologic therapies has been calculated by NICE in a costing template as 2.4%.
- ◆ Juvenile idiopathic arthritis (JIA): children and young people with JIA are significantly fewer than the numbers of adults with RA. JIA is a relatively rare illness, with an estimated incidence in the UK of 1:10,000 children and young people and equates to 1,000 new cases per year. About 10,000 children in the UK are affected ((NICE, 2002) for classification of JIA see Appendix 8).
- ◆ Other musculoskeletal conditions treated with biologic drug therapies that are as yet being used outside their licensed indications include rarer conditions such as systemic lupus erythematosus (SLE) and systemic vasculitis (SV), where there is an emerging evidence base for benefit with B-cell depleting drugs such as rituximab rather than the anti-TNF drugs. There are also on-going clinical trials exploring the therapeutic potential of co-stimulatory blockage such as abatacept in the management of SLE.
- ◆ Other long term conditions treated with biologic therapies include skin conditions such as psoriasis and inflammatory bowel conditions such as Crohn's disease (CD).

## Selecting patients for treatment

To ensure eligible patients are selected to receive biologic therapies, you should undertake a risk benefit analysis of each patient based upon:

1. fulfilment of disease specific treatment criteria as outlined by the BSR and the NICE/SIGN guidance, or
2. exceptional reporting form. Where patients do not fulfil the BSR criteria for treatment, but are considered eligible by their prescribing physician, the physician's reasons for this decision should be clearly documented and supporting evidence provided – this usually will require completion of documentation (referred to as an exceptional reporting form/exceptionality or exception reporting form/concessionary use form). This form must outline the exceptional circumstances that justify the need for treatment and is then submitted for consideration by the funders/commissioners to make the final decision on funding
3. screening to ensure that specific drug inclusion/exclusion criteria have been reviewed according to the specific drugs SPC and licensed indications. An overview of key factors that need to be considered for exclusion criteria is outlined in Workbook section 1 (Appendix 1) but briefly, include:
  - allergic reactions or sensitivity to any of the constituents of the therapy being considered
  - active infections including history of recurring or persistent infections or underlying conditions that may predispose to infections (e.g. chest infections or previous septic joint in situ)
  - tuberculosis
  - women who are pregnant or breastfeeding (effective contraception must be used by both sexes to prevent a pregnancy whilst on treatment)
  - active malignant disease.

The patient should be assessed using a thorough patient-centred consultation which enables practitioner and patient to fully explore issues in relation to the treatment and the effect upon the individual's health, quality of life and activities of daily living. This includes:

- the patient's physical and mental health – this assessment should be supported by medical colleagues

- consideration of the patient's social and psychological needs in the context of the treatment pathway
  - their preferences, anxieties and needs in the context of information sharing
  - consideration of the family or significant others views (if the patient wishes)
  - the level of social support and other contributing factors that may affect the patient's ability to cope with treatment
  - ensuring the patient is able to make an informed decision about their treatment options
  - full education about the potential risks and benefits of treatment (given to the patient in written and verbal form, including information about the drugs (see Appendix 4)).
4. an informed decision. Patients must be guided so they can make an informed decision, and you must ensure that:
    - the patient has a clear understanding of the criteria that will be used to assess the benefits of their treatment and the criteria for cessation of treatment
    - if the patient is unable to give their consent, the registered practitioner must act in accordance with the Mental Capacity Act (2007) and document in the patient's notes why they believe the procedure to be in the patient's best interests, including any involvement from other health professionals, family or carers in reaching that decision
    - consent has been sought and documented for any research or observational data collection (e.g. for the BSRBR). Confirm that a patient consent form is completed for any data collection – either complete the BSRBR/relevant documentation, or liaise with their physician to support its completion
    - the risks and benefits of treatment including contraindications whilst on treatment (e.g. pregnancy) have been discussed and the patient has had an opportunity to ask questions and consider any personal issues
    - the patient is aware of their responsibilities to attend for monitoring of the treatment's effects and to report any infection.

You must further ensure, as part of your assessment, that:

1. the patient, where appropriate, is given the opportunity to select their preferred route of drug administration
2. when the patient has received sufficient information and consents to treatment, national and local trust policy consent forms are signed (where required) and the patient's informed consent documented in their medical notes
3. the co-prescription of MTX with anti-TNF $\alpha$  therapies is either part of the licensed indication (adalimumab, etanercept, infliximab, rituximab) or advocated to enhance treatment effect. In some cases, patients who are intolerant to or have experienced an adverse reaction to MTX will require an alternative disease modifying drug although this will be outside the licensed indication
4. there is local availability of the drug for eligible patients, at the correct dosage – i.e. that there are no financial or other constraints on drug availability in your trust. For some cases, funders require completion of a specific funding request form. These vary from region to region (for an example refer to [www.rcn.org.uk/rheumatology](http://www.rcn.org.uk/rheumatology))
5. for therapies that require subcutaneous self-administration, a training plan and assessment of the patient's ability to self administer are carried out (Appendix 4)
6. if patients decline treatment, are not eligible for it, or cannot start treatment because of constraints on prescribing, you provide them with full guidance and support
7. you review the exclusion/inclusion criteria for the specific drug therapy being considered.

## Disease-specific assessment and management

1. Rheumatoid arthritis
2. Ankylosing spondylitis
3. Psoriatic arthritis

Refer to the core exclusion criteria outlined in general screening and assessment section (page 10) for all diagnoses.

### 1. Rheumatoid arthritis: assessment of patients before and during treatment

Before the patient's treatment begins, and during ongoing treatment, specialist practitioners should test and monitor the following:

#### Disease activity

- ◆ Fulfils the criteria for active RA.

#### For anti-TNF $\alpha$ therapy

The BSR is advocating a change to using the Disease Activity Score (DAS) 28 eligibility and response criteria for treatment with anti-TNF $\alpha$  therapies and should these be endorsed, information can be accessed from the BSR website ([www.rheumatology.org.uk](http://www.rheumatology.org.uk)) (accessed 03/06/09). The BSR propose a disease assessment criteria of a DAS 28 of greater than 3.2 measured with at least three or more tender and three or more swollen joints. However, at the time of going to print, NICE eligibility criteria differ and are outlined below.

Practitioners should refer to both the BSR guideline link to review the final ratified guidelines and also the latest guidance from NICE for eligibility criteria.

The response criterion is defined by the Eular 'moderate' or 'good' response (see Appendix 6, *Eular Response Criteria*). Your local policy/agreements must guide clinical decision making until NICE respond to the BSR's proposal. In the meantime, refer to the BSR for further information and guidelines.

The criteria stipulated by NICE for the prescribing of TNF inhibitors for RA are, at the time of going to press:

- ◆ active RA as measured by DAS 28 joint count scoring >5.15 on two occasions (one month apart) before treatment
- ◆ the patient has undergone a trial of two disease modifying anti-rheumatic drugs (DMARDs) including MTX (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

#### Treatment response for anti-TNF $\alpha$ therapy

- ◆ The BSR and NICE recommend that a full disease activity assessment is repeated after six months of treatment. In the six month assessment it is important to consider other factors that may have a negative or positive influence on the DAS – for example temporary cessation of treatment for

surgery may adversely affect the DAS. Consider a repeat DAS once the patient is re-established on treatment.

- ◆ NICE criteria stipulate that ongoing six monthly DAS assessments should be continued to assess treatment benefits. Treatment should be withdrawn if an adequate response is not maintained.
- ◆ Be cautious in interpreting the DAS. Document any key changes in management that may have an impact on DASs and affect treatment response – for example temporary cessation of treatment or withdrawal of long term steroid therapy. Additional DASs may be required in some circumstances (for example, following a flare up, infection, injury, or surgery).

#### For rituximab for RA

- ◆ Treatment with rituximab is recommended as an option for adults with severe active RA who have had an inadequate response to, or intolerance of, other DMARD, including treatment with at least one anti-TNF $\alpha$  (NICE, 2007c).

#### For other biologic therapies

- ◆ Abatacept and anakinra have not been recommended for use in England, Scotland or Wales by NICE or SIGN. See section on intravenous infusions for further information on abatacept.
- ◆ Treatment criteria for second generation anti-TNF $\alpha$  therapies and other biologic agents such as certolizumab pegol are subject to licensing decisions and final determinations by authorities such as NICE and SIGN. Refer to treatment criteria as and when SPC and guidance documents are published ([www.scottishmedicines.org.uk](http://www.scottishmedicines.org.uk), [www.nice.org.uk](http://www.nice.org.uk)).

## 2. Ankylosing spondylitis: assessment of patients before and during treatment

It is important to ensure you have good liaison with physiotherapy colleagues who have expertise in the assessment of AS. Undertake core assessment and screening as well as looking at the disease specific aspects including:

1. the same general exclusion criteria as for patients with RA
2. the patient should satisfy the modified New York diagnostic criteria for AS (refer to [www.nass.co.uk](http://www.nass.co.uk) for further information)
3. the patient should fulfil NICE eligibility criteria

(NICE, 2008b) for evidence of active disease. These include measurements using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (see below), and failure to control symptoms despite conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated dosage for four weeks.

Before the patient's treatment begins, and during ongoing treatment, specialist practitioners should test and monitor the following:

#### Disease activity

- ◆ BASDAI score of at least four units and at least 4cm on the 0-10cm spinal pain visual analogue scale (VAS) on two occasions at least 12 weeks apart without any change in treatment.
- ◆ Where the BASDAI or spinal pain VAS is not a clinically appropriate tool (for example, where a patient has linguistic, learning or other disabilities that limit their ability to respond/communicate), use another method of assessment to suit the patient's circumstances while demonstrating the clinical need.

#### Treatment response

- ◆ NICE recommends that response to treatment should be assessed 12 weeks after the treatment has been initiated and that treatment should be continued in the presence of an adequate response. An adequate response is a reduction in the BASDAI score to 50% of the pre-treatment value or by two or more units and a reduction of the spinal pain VAS by 2cm or more.
- ◆ Patients who have experienced an adequate response should have their condition monitored at 12 week intervals, if a response is not maintained a repeat assessment should be made after a period of six weeks. Treatment should be discontinued at this time if the response has not been maintained.
- ◆ Blood tests prior to commencing treatment (as outlined in *Screening and risks* section, page 9).

#### Other tools used to assess AS include:

- ◆ Bath Ankylosing Spondylitis Metrology Index (BASMI)
- ◆ Bath Ankylosing Spondylitis Fatigue Index (BASFI)

Note: All AS documents and scoring information can be accessed at [www.nass.co.uk](http://www.nass.co.uk).

See also: *Adalimumab, etanercept and infliximab for ankylosing spondylitis* (NICE, 2008b).

### Withdrawal of therapy

NICE guidance states that patients who fail to gain adequate response to treatment following the 12 week and subsequent six week review must stop treatment.

Guidelines for withdrawal of anti-TNF $\alpha$  treatment due to adverse events will be the same for AS patients as those outlined for RA adverse events (see *specific screening and monitoring issues* section 2, page 10).

### 3. Psoriatic Arthritis: assessment of patients before and during treatment

You will need good liaison with a dermatology department to aid assessment of the patient's skin, including expertise in undertaking skin scores Psoriatic Area Severity Index (PASI) and annual skin malignancy check.

You should undertake core assessment and screening as well as considering the disease specific aspects including:

1. fulfilment of NICE eligibility criteria for PsA (NICE, 2007a; NICE, 2008c)
2. the same general exclusion criteria as for those patients with RA
3. disease activity.

#### Disease activity

Patients must have active disease demonstrated as follows, and have had adequate therapeutic trials of at least two standard DMARDs:

Disease activity	Therapeutic trial of DMARDs
Patient has peripheral arthritis with three or more tender joints and three or more swollen joints assessed using a 78/76 joint count, on two separate occasions at least one month apart.	Patient has had treatment with a minimum of two DMARDs (either individually or in combination) for at least six months, of which two months is at standard target dose (unless intolerance or toxicity limits dose).

Although not a requirement in the NICE guidance, the BSR recommends, from a clinical perspective that evaluation of patients with PsA should also include a skin assessment called the PASI (Kyle *et al.*, 2005). The PASI is a scoring system that can be used to record the treatment response achieved by assessing changes in the patient's psoriasis. Expert support from your dermatology department will be helpful for patients with severe psoriasis as well as PsA. Educational tools to

advise on how to score the PASI based upon skin changes have been produced by a number of pharmaceutical companies.

#### Exclusion criteria

- ◆ Special caution should be taken in PsA patients with active psoriasis who have received >1000 joules cumulative dosage of Psoralen and Ultraviolet A therapy (PUVA) who have subsequently been treated with ciclosporin for at least one year. There is thought to be a high risk of developing non-melanoma skin cancer in such cases. Annual skin checks are recommended for malignancy, these should be performed by a dermatology specialist.
- ◆ HIV-positive/AIDS patients.

#### Treatment response

Clinical response measured using the Psoriatic Arthritis Response Criteria (PsARC) should be carried out at three months following initiation of therapy. Response is defined as improvement in two factors, at least one of which should be a joint score. There should be no worsening of any of the measures:

- ◆ patient global assessment on a 0-5 Likert scale
- ◆ physician global assessment on a 0-5 Likert scale (with improvement defined as a decrease by at least one unit, worsening defined as an increase by at least one unit)
- ◆ tender joint score
- ◆ swollen joint score (response is defined as decrease of at least 30%; in one of the joint scores, worsening defined as an increase of at least 30%).

#### Withdrawal of therapy

Guidelines for withdrawal of anti-TNF $\alpha$  treatment for patients with RA will apply to patients with PsA who experience adverse events.

**Example for working out Psoriatic Arthritis Response Criteria (PsARC)**

	Date 1 Start	Date 2 3 months	Percentage improvement Score on Date 1 minus score on Date 2 Divided by Score on Date 1 x 100% i.e. $1 - 2 \div 1 \times 100\%$
Number of swollen joints			
Number of tender joints			
	Date 1	Date 2	Absolute improvement in Likert Score
Patient global assessment			
Physician global assessment			

## Screening and risks

This section provides advice on the issues to consider for all patients being prescribed a biologic therapy. There are also notes on particular drug therapies highlighting specific screening and monitoring issues for that treatment.

### 1. Pre-treatment screening and monitoring

For both first generation (adalimumab, etanercept and infliximab) and second generation anti-TNF $\alpha$  therapies (certolizumab pegol and golimumab), blood monitoring should be undertaken before starting treatment. The minimum monitoring required should fulfil the criteria for monitoring of MTX or other DMARDs which are co-prescribed with biologic therapies (refer to BSR (2008) Guidelines [www.rheumatology.org.uk](http://www.rheumatology.org.uk)) (Chakravarty *et al.*, 2006).

Auto-antibodies are not routinely taken before commencing treatment, but may be necessary if the patient develops symptoms suggestive of lupus.

Before starting treatment, take the following:

- ◆ chest x-ray, performed and reviewed by the prescribing physician (Grade of recommendation C)
- ◆ full blood count (FBC)
- ◆ urea and electrolytes (U&E)

- ◆ liver function tests (LFT)
- ◆ test for hepatitis B and C (Furst *et al.*, 2008), if risk factors present (Grade of recommendation C) (for hepatitis C risk factors, refer to assessment tools and advisory documents at [www.nhs.uk](http://www.nhs.uk))
- ◆ human immunodeficiency virus (HIV) if risk factors (Grade of recommendation C)
- ◆ HBV if risk factors (Grade of recommendation C)
- ◆ antinuclear antibodies (ANA), if indicated (this test not required for AS)
- ◆ DNA binding.

### 2. Specific screening and monitoring issues

#### Blood dyscrasias

Neutropenias, pancytopenias and aplastic anaemias have been observed in patients on anti-TNF $\alpha$  therapies. The numbers are small and it may be difficult to know whether these are a direct side-effect of the anti-TNF $\alpha$  or due to current or previous DMARD therapy. However, practitioners should ensure the patients are encouraged to report signs suggestive of blood dyscrasias (e.g. bruising, bleeding and persistent fever) and that vigilance is applied during routine monitoring. You should request an immediate FBC if the patient is unwell (Grade of recommendation C). Abnormal blood results should be repeated and reviewed promptly –

depending upon the trend of blood results, it may be necessary to temporarily withhold treatment until these results have been reviewed and discussed with the prescribing physician (Grade of recommendation C).

### **Anakinra**

Do not administer anakinra in patients with a neutropenia ( $<1.5 \times 10^9/l$ ). Neutropenias have been reported in those treated with anakinra (Amgen, SPC, 2008). If patients develop neutropenia whilst on treatment, stop treatment, refer to prescribing physician and monitor closely.

### **Etanercept in combination with sulfasalazine**

Reports of significantly decreased mean white blood cell count were seen in patients who were stable on sulfasalazine and were then treated with etanercept.

### **Rituximab**

In addition to routine pre-screening, test for baseline immunoglobulin levels (IgM) as decreased levels of IgM have been identified in those treated over time (Smolen, 2007).

### **Tocilizumab**

In addition to routine pre-screening, lipid profiles should be checked. Elevated lipids should respond to lipid lowering agents if required. Show caution if initiating treatment in a patient with any of the following: consistently low neutrophils ( $< 2 \times 10^9/l$ ) or platelet counts ( $< 50 \times 10^9/l$ ) or raised LFT  $> 1.5 \times$  Upper Limit of Normal (ULN).

### **Anti-nuclear antibodies (ANA) and anti-double stranded deoxyribonucleic acid (anti-dsDNA)**

Patients have developed ANA and anti-dsDNA antibodies following treatment with anti-TNF $\alpha$ . For this reason, pre-treatment tests for ANA are recommended. In a few cases patients have developed new onset SLE or lupus-like syndromes. Such symptoms have usually resolved once treatment is discontinued, and no patients have developed lupus nephritis or central nervous system symptoms. The range of those that converted from negative to positive titres was approximately 11% for compared to 5-8% in placebo group (SPCs of anti-TNF $\alpha$  therapies). The impact of the auto-antibody response and long term treatment is unknown.

Development of auto-antibodies, rare cases of cutaneous vasculitis or lupus-like syndromes should

necessitate withholding treatment and seeking advice from the prescribing physician.

When treating with other biologics, note that abatacept studies have not identified a significant trend in the development of ANA or anti-dsDNA. Studies of tocilizumab identified 1.9% of patients treated developing auto-antibodies in those not co-prescribed a DMARD (Nishimoto *et al.*, 2007).

### **Antibodies to biologic therapies**

**Human antihuman antibodies (HAHA):** Antibodies may develop in patients against an injected antibody. Biologic therapies are developed from monoclonal antibodies that have been biologically engineered using technology that combines either fully human or part human proteins to either an immunoglobulin or a receptor. A patient may, as a result, develop antibodies to the subcutaneous or intravenous therapy based upon whether the component parts are made up of HAHA or human anti-chimeric antibodies (HACA). Neutralising antibodies will reduce the therapeutic benefit of the treatment.

The development of neutralising antibodies to the therapy are associated with treatment-related reactions and loss of efficacy. There is the potential for therapies to precipitate an immunological response that results in antibodies against the therapy itself, increasing the risk of drug related reactions or reduced therapeutic benefit. Antibodies have been detected in all therapies although, to date, neutralising antibodies have not been detected in etanercept.

**HACA:** Monoclonal antibodies may have a mammalian component (e.g. mouse or hamster) or be fully human. An immunological response to the chimeric (mammalian/mouse) component of some biologic therapies can result in HACA being detected in post-treatment patients. The presence of HACA may be associated with a greater risk of infusion/allergic reactions or a reduced treatment benefit in therapies such as infliximab and rituximab. Delayed hypersensitivity reactions have also been reported with infliximab when intervals between treatments are increased.

The potential for HACA to develop must be considered in all treatments that have a chimeric monoclonal antibodies component. These include:

- ◆ infliximab
- ◆ rituximab.

Co-prescription of MTX can significantly reduce the incidence of antibodies developing.

### 3. Blood monitoring while on treatment

In most cases, patients will be co-prescribed a DMARD (usually MTX). Therefore the minimum blood tests required will be those recommended for monitoring of MTX or alternative prescribed DMARD. The BSR guidelines stipulate monthly blood tests for those established on MTX, but it may be possible to reduce this frequency, depending on local policy/agreed guidelines – and importantly upon the patient's individual risk factors/co-morbidities.

Reports from the SPCs of all biologic therapies identify changes in the blood picture, although the vast majority of these are uncommon and it is not clear whether they can be directly attributed to the biologic therapy. However, there have been reports of important and potentially life threatening changes in the blood picture of those treated with anti-TNF $\alpha$  therapies.

If you see abnormal blood results either before initiating treatment or during treatment with any biologic therapy, you must repeat blood tests if necessary and seek guidance from the prescribing physician.

For intravenous therapies, a recent FBC, LFT and U&E should be reviewed before treatment. For some therapies pending license, additional monitoring may be required (e.g. lipid profile for tocilizumab). Refer to the SPC.

#### Additional screening points

Specific screening and monitoring points for different biologic therapies are outlined below:

#### B cell depletion therapy (rituximab) screening

- ◆ IgM levels.
- ◆ CD19 may be considered.
- ◆ Ensure patient has not been vaccinated within last four weeks before treatment commences.

#### IL-6 receptor blocker (tocilizumab) screening

Early research studies have identified increases in liver enzymes, particularly for those patients co-prescribed MTX. The changes were identified as a 'saw tooth effect' rising and falling between infusions (Maini *et al.*, 2006). Raised serum lipid levels were seen initially but stabilised during the research study periods (the significance of raised lipids appears to reflect other anti-inflammatory agents and may be related to the

decrease in c-reactive protein (CRP)). Decreases in neutrophils have been seen in a small number of patients treated with Tocilizumab. Neutrophils returned to normal levels when treatment was withdrawn. Treatment should be considered with caution in those who have a low neutrophil count (Absolute Neutrophil Counts  $<2 \times 10^9/l$ ) (Emery *et al.*, 2008).

Refer to the SPC guide when published. Until either the SPC or further evidence is available, screening should be considered the same as for other anti-TNF $\alpha$  therapies with the addition of:

- ◆ lipid profiles and cardiovascular risk factors – may require standard management before starting treatment.

Discuss with the prescribing physician if history of:

- ◆ severe allergic or anaphylactic reaction to previous monoclonal antibodies
- ◆ current hepatic disease or impairment.

Routine blood monitoring of tocilizumab should consider:

- ◆ initial rise in liver function tests – should normalise within the first six months of treatment
- ◆ increase in total cholesterol (although lipid ratio remains unchanged) in the first four weeks of treatment
- ◆ transient neutropenia – can occur during the first 4-5 infusions.

### 4. Risk of infection: general areas for caution

There is an increased risk of serious infections for all patients who are treated with immunosuppressant therapies, including patients with RA taking MTX. Until further evidence is available, you must take into account the risk of bacterial infections with all biologic therapies (including currently unlicensed biologic therapies). There appears to be an increased incidence of infection when biologics are co-prescribed with a corticosteroid. There is also a low, but important, risk of opportunistic infections including fungal infections for all biologic therapies (Grade of recommendation C). Skin and soft tissue infections are the **type** of infections most frequently identified as serious infections yet respiratory tract infections are the most common **site** of identified infections.

All patients being considered for a biologic therapy must be screened to exclude the risk of any infection, including TB (see page 13 for more detail on TB). If

serious infections are evident before treatment, they should be reviewed by the prescribing physician and fully resolved before considering treatment with a biologic (Grade of recommendation C). If a serious infection develops, treatment should be stopped and only restarted once the infection has completely resolved. Ensure the patient is aware of their own responsibility for reporting any clinical signs and symptoms that might indicate an infection.

All RA patients have a higher risk of infection and mortality rate than the general population, which must be borne in mind in context of all drug therapies. It is therefore essential to maintain a high index of suspicion of infection, and screen appropriately (e.g. dipstick urine, chest examination, etc).

#### Points to look out for:

- ◆ practitioners should be aware of symptoms suggestive of systemic infections (fever, malaise, weight loss, sweats, cough, or dyspnoea) and seek medical advice promptly
- ◆ a number of serious infections have been described with anti-TNF $\alpha$  therapies and these include lower respiratory tract infections (the most common site of infection) followed by those involving skin and soft tissues. The adjusted relative risk of serious infections from early evidence published from international observational registries (German, Swedish and UK) range from 1.4 to 4.6 per 100 patient-years (Dixon *et al.*, 2007) (Grade of recommendation B)
- ◆ pneumocystis jiroveci pneumonia (PCP) has been reported with adalimumab, etanercept and infliximab, and appears to correlate with the co-prescribing of high doses of glucocorticoids (Grade of recommendation C)
- ◆ there have also been rare reports of histoplasmosis, candidiasis, listeriosis, pneumocystis carinii and aspergillosis with pneumonia being the most common presentation
- ◆ patients should be advised on avoidance of foods that may increase the risk of food borne infections (e.g. listeria or salmonella). Foods to avoid include: unpasteurised foods such as milk and dairy products including cheeses (soft, blue, goat and feta), undercooked meats or raw eggs (Grade of recommendation C)
- ◆ patients > 65 years of age demonstrated a higher incidence of infections when treated with abatacept (Bristol Myers Squibb, Orencia, SPC, 2007)
- ◆ increased risks of serious infections (but not opportunistic infections) have also been seen in patients treated with rituximab as with biologic therapies.

#### Infections which contraindicate treatment

Biologic therapies should not be initiated or resumed in the presence of serious infection. This includes bacterial and fungal infections requiring treatment (Grade of recommendation C). Discuss with a prescribing physician if patients have or develop:

- ◆ bacterial infection receiving treatment with antibiotics or requiring treatment, including upper respiratory tract infections
- ◆ suspicion of TB (see page 13)
- ◆ HIV or risk of HIV
- ◆ active herpes zoster infections
- ◆ clinically significant fungal infections
- ◆ non-healed infected skin ulcers
- ◆ HBV: treatment for those with chronic HBV may not be contra-indicated if prior or concurrent anti-viral treatment – seek medical guidance as assessments may be required for evidence of significant liver injury
- ◆ hepatitis C: treatment with anti-TNF $\alpha$  for those with hepatitis C infection (regardless of whether this is with or without concurrent viral treatment) appears to be safe but should be monitored closely (Grade of recommendation C). Treatment may be positively beneficial in cases where hepatitis C infection is associated with chronic cryoglobulinemia. There have been reports of the condition worsening following treatment with anti-TNF $\alpha$  (Wyeth, Enbrel, SPC 2008). Discuss with prescribing physician and if treated ensure close monitoring of serum aminotransferases (see also HBV)
- ◆ respiratory symptoms that suggest an infection and /or taking a high dose of steroids. Note, prophylaxis may be required
- ◆ other infections: discuss with physician if these are identified, for example, HIV, as evidence remains controversial and therapy is not usually recommended in these cases (Grade of recommendation C)
- ◆ chicken pox: if patient's immune status has not been established and the patient is exposed to Varicella Zoster virus (chicken pox), check their immune status. For those who develop chicken pox or

shingles – stop treatment (biologic and MTX) and seek medical guidance on appropriate treatment with anti-viral drugs such as acyclovir.

## 5. Risk of infection: Tuberculosis

There is a recognised increased risk of reactivation of latent TB when disarming the immune response of TNF $\alpha$ . The risk of TB reactivation has been significantly reduced as a result of thorough screening for risks of TB. Until there is long term evidence to confirm or dispute the risks of TB for other biologic therapies, a review of risks related to TB reactivation and ongoing vigilance should be applied to all biologic therapies (Grade of recommendation C).

The BSRBR reports an increase risk of latent TB for those treated with anti-TNF $\alpha$  therapies, with most cases having had evidence of previous exposure to TB. Studies have identified an up to sevenfold increase in the risk of TB in circumstances where screening and management recommendations in relation to TB fail to be implemented appropriately (Gomez-Reino *et al.*, 2007).

Although interpretation of preliminary evidence published by the BSRBR should be treated with caution, evidence to date suggests there may be differences between the anti-TNF therapies, with adalimumab and infliximab having a slightly higher risk of TB than etanercept. However, until further evidence is available patients on all anti-TNF $\alpha$  therapies must be treated with the same level of vigilance when screening for TB (BSR, 2009; Dixon *et al.*, 2007). Most cases of TB reported with infliximab occurred within the first six months of treatment. For detailed guidance refer to Ledingham *et al.*, (2005), and BSR guidelines (pending publication).

### First generation anti-TNF $\alpha$ therapies

All first generation anti-TNF $\alpha$  (adalimumab, etanercept, infliximab) have shown an increased risk of TB or reactivation of latent TB. There is also an increased risk for those also receiving corticosteroids (Furst *et al.*, 2008). Patients with active, latent TB or those with an identified high risk of latent TB or significant prior exposure should not be started on anti-TNF $\alpha$  therapies until they have been adequately treated or reviewed by a specialist in the management of TB (Grade of recommendation C). If a patient has any history of TB exposure, respiratory specialist screening and/or treatment will be required (see Appendix 5).

### Second generation anti-TNF $\alpha$ therapies

In the case of second generation anti-TNF $\alpha$  therapies (pending licensing) (certolizumab pegol, golimumab) further evidence is awaited, but in the meantime the screening guidelines outlined for first generation anti-TNF $\alpha$  therapies should be applied. This is despite the fact that initial research evidence of golimumab did not identify new cases of TB for those patients who were naïve to biologic therapies (Kay *et al.*, 2008). Research trials apply rigorous criteria for assessing, screening and excluding patients who were at risk of tuberculosis which may not truly reflect routine clinical practice.

### TB screening

For detail of TB screening, refer to British Thoracic Society (BTS) TB guidelines (2005).

Before treatment starts, every patient should be screened for TB including:

- ◆ full patient history
- ◆ checking for evidence of BCG scar
- ◆ checking for evidence of contact by the patient and/or history of TB among family members
- ◆ physical examination and chest x-ray at least six months before starting treatment unless there are current respiratory problems, in which case a repeat chest x-ray would be required. Chest x-rays must be reviewed by a physician
- ◆ additional tests such as tuberculin skin test (TST), blood based diagnostic assays, IFN-ELISPOT assay (Quantiferon TB gold or T-spot TB) tests have been shown in early data to be of value in evaluating people with latent TB, and possibly in those who have received prior immunisation from BCG. However, evidence should be considered in the context of specific local population needs and screening issues together with the costs (costs range from £35 – £100 per test) when considering the widespread use of such investigations
- ◆ active TB must be adequately treated before anti-TNF $\alpha$  therapy can be commenced (Grade of recommendation C).

### Screening for TB with other biologics (non anti-TNF $\alpha$ therapies)

#### Abatacept (T cell costimulation blockade)

Abatacept screening in clinical trials excluded any patients screened positive for TB. The SPC advocates screening for TB and vigilance in monitoring for signs

suggestive of TB. Refer to the general screening guidance as advocated for anti-TNF $\alpha$  therapies.

### Anakinra

There is no evidence for increased risk of TB in anakinra (BSR, 2009).

### Rituximab (anti-CD 20 B cell depletor)

To date rituximab does not appear to increase risks related to reactivation of TB (Smolen, 2007).

Treatment with rituximab and other biologic therapies has to date been given to a patient when anti-TNF $\alpha$  therapies have failed. This means that patients will have already undergone a rigorous TB screening process before treatment with an anti-TNF $\alpha$ . The SPC for rituximab does not stipulate screening for TB. Studies of rituximab in the treatment of non-Hodgkin's lymphoma (NHL) have shown no increased incidence of TB – although patients recruited for research trials are rigorously screened and non-suitable patients excluded, so the trial may not reflect the profile of patients in routine clinical practice. To date there are no reported incidents of TB (with the exception of one case in a T-cell deficient HIV infected patient – reported in a personal communication Roche Laboratories 19th September, 2008).

Nevertheless, it is essential that practitioners maintain a high index of suspicion in relation to the individual patient's history, risk factors and any indications that might highlight recurrence of latent TB. One point of particular note is that rituximab treatment requires two pulses of glucocorticosteroids co-prescribed with MTX. It is therefore essential to maintain a high level of vigilance.

### Tocilizumab (IL-6)

The preliminary evidence does not suggest a risk of re-emergence of latent TB infections with the inhibition of IL-6. IL-6 does not have a pivotal role in granulomatous containment such as that of TNE, although vigilance should be maintained until further long term evidence is available. Pending licensing indications, further studies and screening guidance, practitioners should ensure a high index of suspicion is maintained and screening should be undertaken as outlined for anti-TNF $\alpha$  therapies.

### Ongoing monitoring for TB

All patients on biologic therapies should be closely monitored for any signs of TB and other infections. TB

monitoring should continue throughout and for six months after discontinuing treatment. Clinicians should have a high index of suspicion in relation to re-emergence of latent TB following treatment with a biologic therapy, particularly anti-TNF $\alpha$  therapies (Grade of recommendation C).

If a patient develops a productive cough or haemoptysis, weight loss and fever, their sputum should be tested for acid fast bacilli (AFB). Biologic therapies should be withheld until the results are available and inform the prescriber/rheumatologist.

If TB is confirmed during treatment, full anti-TB chemotherapy must be commenced in discussion with a TB specialist. In some circumstances where clinically indicated by the prescribing physician, and where the patient consents, anti-TNF $\alpha$  can continue whilst on anti-TB chemotherapy (Grade of recommendation C).

Patient information leaflets about TB with anti-TNFs and immunisation are available in a number of languages from: [www.immunisation.nhs.uk](http://www.immunisation.nhs.uk).

## 6. Immunisation

Live vaccines *should not* be administered to immunocompromised patients (Grade of recommendation C). This includes patients treated with biologic therapies.

Immunocompromised status includes patients:

- ◆ receiving systemic high-dose steroids (>40mg/day) although those on lower doses may also be immunocompromised and at increased risk of infections (DH, 2006)
- ◆ treated with DMARDs including: azathioprine, ciclosporin, MTX, cyclophosphamide, leflunomide and biologics. Patients treated with the specified DMARDs alone or in combination with steroids until at least six months after terminating such treatment.

Live vaccines include:

- ◆ varicella zoster
- ◆ mumps, measles and rubella
- ◆ yellow fever
- ◆ oral typhoid
- ◆ oral polio.

### Live (attenuated) vaccines

If live vaccines are required they should be administered at least four weeks prior to commencing

any biologic therapy. On cessation of treatment live vaccines may be administered, provided the drug has been effectively cleared from the body (clearance should be based upon at least three cycles of the drug's treatment half life) or in any case at least six months after cessation of treatment. The half life of a drug is documented in the SPC and this timeframe needs to be multiplied by three to ensure total clearance of the biologic. Seek guidance from a pharmacist, local medicines information unit or refer to the SPC guidance (Grade of recommendation C).

### Inactivated vaccines

Limited published evidence suggests that an acceptable but sub-optimal immunological response is to be expected to influenza and pneumococcal (pneumovax) for patients treated with first generation anti-TNF $\alpha$  therapies and rituximab, especially when co-prescribed with MTX (Oren *et al.*, 2008; Kapetanovic *et al.*, 2006). Pneumococcal and annual influenza vaccinations should be offered to patients on biologic therapies (Grade of recommendation C).

A strategy to achieve the optimum in care for those with inflammatory joint disease is for practitioners to identify the patient's immune status whilst planning their treatment plans and care pathway. This will mean patients are adequately prepared and do not have to wait before requiring biologic therapies. In particular, consider the patient's status before starting treatment and where indicated ensure:

- ◆ vaccinated for pneumococcal vaccination (inactivated)
- ◆ vaccinated for hepatitis B (inactivated) for patients at high risk of disease present and vaccination not previously administered (Saag *et al.*, 2008)
  - hepatitis B vaccination has very few contraindications to administration. In the adult population 10-15% fail to respond to three doses of vaccine. Immunocompromised patients may achieve only a suboptimal response to immunisation. Refer to immunisation guidance from the Department of Health or seek local specialist advice if required (DH, 2006)
  - review herpes zoster status – immunocompromised patients should not receive **any** live (attenuated) vaccinations including varicella vaccination. Varicella zoster immunoglobulin (VZIG) is recommended for the immunocompromised patient if they have:

- had significant exposure to chicken pox or herpes zoster
- a clinical condition that increases the risk of severe varicella (including immuno-suppressed patients)
- no antibodies to VZ virus and have had exposure that warrants evaluation of status. If antibody status is unknown, then test. If results cannot be available within seven days from exposure, patients should receive VZIG without testing. If antibody status is known and is positive VZIG is not indicated (DH, 2006).

(Grade of recommendation C).

For detailed guidance refer to the Department of Health website [www.dh.gov.uk](http://www.dh.gov.uk) – or Immunisations Green Book (2006).

### Other biologics

#### Abatacept

The SPC states that live vaccines should not be administered within three months of discontinuing treatment. There is insufficient data to advise on the response to vaccinations whilst on abatacept.

#### Anakinra

Patients treated with anakinra who received anti-tetanus antibody vaccine demonstrated equivalent response between treated and placebo patients (Amgen, Anakinra SPC, 2008).

#### Unlicensed therapies

There is as yet no guidance on unlicensed therapies (certolizumab pegol or golimumab). Refer to the SPC but in all circumstances apply at least the guidance outlined for anti-TNF $\alpha$  therapies and withhold all live vaccines whilst on treatment until further evidence is available.

Patients who have been treated with rituximab may have an insufficient response to the influenza vaccine 87-150 days after treatment (BSR, 2009).

## 7. Cardiac function

### Anti-TNF $\alpha$ therapies

A clinical examination should include an assessment of cardiac function to exclude heart failure, because of the potential detrimental effect of anti-TNF $\alpha$  therapy on patients with severe heart failure. Examine, for example, for signs of ankle oedema or symptoms of breathlessness – breathlessness may indicate respiratory problems but could also indicate heart failure. If there are symptoms suggestive of heart failure, review with prescribing physician. If the patient shows symptoms of poor cardiac function, refer them to their prescribing physician.

If evidence of chronic cardiac failure (CCF) develops or increases during treatment with anti-TNF $\alpha$ , stop treatment and review with prescribing physician (Grade of recommendation C). The balance of risk against benefit must be considered on a case by case basis, and treatment must be stopped and discussed with the prescribing physician if there is no clear benefit, even when the CCF remains stable during treatment (Grade of recommendation C). For guidance on NYHA classification revised criteria (1994) refer to [www.americanheart.org](http://www.americanheart.org). Patients should not be started on treatment if they have a NYHA criteria grade III or IV (Grade of recommendation C).

### Infliximab

Infliximab is contraindicated for patients with moderate or severe heart failure (NYHA class III/IV).

### Other drug therapies

Patients who are eligible for other biologic therapies because previous treatment with an anti-TNF $\alpha$  has not been successful, will already have been subject to a full cardiac screening. However, this should not preclude routine medical examination and review of cardiac function when initiating a new therapy.

### Rituximab and abatacept

To date evidence has not identified an increased risk of cardiac complications related to rituximab or abatacept.

### Certolizumab pegol and golimumab

The second generation of anti-TNF $\alpha$  therapies should be considered to have the same risk of cardiac side effects as for the first generation until further evidence is published. However, for as yet unlicensed therapies practitioners should scrutinise the SPC when published to review the relevant evidence.

### Tocilizumab

This drug has been shown to increase lipid parameters. Although the majority of patients did not have an increase in the atherogenic indices, they may require standard treatment with lipid lowering therapy.

## 8. Neurological issues

Rare occurrences of demyelinating syndromes have occurred with anti-TNF $\alpha$  therapies and do not necessarily resolve with treatment withdrawal (Furst *et al.*, 2008). Exclude any personal or family history of demyelinating disease. If there is relevant personal or family history, discuss with the prescribing physician. If the patients shows signs of demyelination (for example, ataxia, paresthesia, facial nerve palsy, optic neuritis, or ascending motor neuropathy), withhold treatment and review with prescribing physician/neurologist (Grade of recommendation C).

### Abatacept

Deterioration in multiple sclerosis patients is a potential theoretical risk with abatacept.

### Rituximab

A small number of cases have been reported of progressive multi-focal leukoencephalopathy (PML) when rituximab is used for an unlicensed indication. The presentation of PML may be related to extensive immunosuppressive therapy or the disease itself (for example, systemic lupus erythematosus). Vigilance in monitoring is therefore advocated until further evidence is published.

### Other biologics

There is no documented evidence of such risks to date – we await licensing indications and SPC. Apply the minimal screening used for anti-TNF $\alpha$  therapies until further evidence is available.

## 9. Surgery

All biologic agents should be withheld peri-operatively, based upon the particular drug therapy's half life. Allowance for full clearance of the therapy from the patient's body before surgery is usually calculated at 3-5 x the drug's half life (Grade of recommendation C) (BSR, 2009). For example, the drug half life for adalimumab is 15-19 days, etanercept is 2.9 days, infliximab is 8-9.5 days. If the timing of surgery were to be considered based on 3 x half life for these three therapies, surgery should not be undertaken until

treatment has been withheld for approximately:

- ◆ adalimumab (45 days, i.e. 3 x15 days)
- ◆ etanercept (9 days)
- ◆ infliximab (24 days).

The potential risks of maintaining treatment during surgery should be balanced against the potential risk of stopping treatment. The risk and benefits should be considered on a case by case basis and in discussion with the patient, prescribing physician and surgical team, but wherever possible treatment should be stopped prior to surgery (Grade of recommendation C).

Evidence remains mixed as to whether anti-TNF $\alpha$  therapies increase the risk of post-surgical infection. The decision to restart treatment should be discussed with the patient, medical and surgical teams once it is clear that healing has occurred, with evidence of good tissue resolution. Minor operations may present a minimal risk that needs to be balanced against the risk of treatment withdrawal flare. The same principles should be applied to other biologic therapies until further evidence is available.

## 10. Malignancy

Patients should be advised that, to date, with first and second generation anti-TNF $\alpha$  therapies there is no evidence for an increased risk of solid tumours above those expected in the general RA population (Grade of recommendation C).

However, the evidence of increased risks of lymphoma, particularly NHL, lung cancer and non-melanomatous skin cancer have been reported as higher in patients with active chronic inflammatory arthritides compared to the general population (Furst *et al.*, 2008; Smitten *et al.*, 2008; Leombruno *et al.*, 2008; Alonso-Ruiz *et al.*, 2008). As a result, the evidence of possible risks related to anti-TNF $\alpha$  remains controversial. All patients should be assessed if there is an index of suspicion for possible malignancy or high risks (for example, in heavy smokers or those with chronic obstructive pulmonary disease (COPD)).

If malignancy occurs while a patient is taking any of the biologic therapies, you should investigate and it may be necessary to cease treatment (Grade of recommendation C). Withhold drug treatment until the situation is discussed with the prescribing physician.

### Skin cancers

The challenges outlined in interpretation of the general risks of malignancy also apply to skin cancers. Patients

should be advised on preventative measures such as skin checks and protection as well as the risk of non-melanoma skin cancers particularly when treated with anti-TNF $\alpha$  therapies (Furst *et al.*, 2008) (Grade of recommendation C).

Ensure patients are encouraged to report any changes in skin appearance suggestive of non-melanoma skin cancer prior to and during treatment and review their history of PUVA use if appropriate. For PsA guidance see page 8.

### Smoking

Smoking contributes to poorer disease outcomes for patients with sero-positive RA and is also an additional risk factor for cardiovascular disease. However, evidence is limited on the risk of developing a further malignancy (such as lung cancer) in patients treated with anti-TNF $\alpha$  who have had a previous malignancy (Grade of recommendation D).

### Abatacept

An increased number of lung cancers have been identified in early studies of the use of abatacept, although the numbers have been considered to be equivalent to the risk of malignancy in the RA population (but not the general population). Caution should be considered in patients with COPD. An increased incidence of lymphomas and mammary tumours were noted in mouse studies – the significance of this is not clear (SPC, 2007). Research trials excluded candidates with malignancy.

### Tocilizumab

Await further evidence.

## 11. Skin

(see also Malignancy section)

There have been reports of psoriatic skin lesions, or exacerbations of those with pre-existing psoriasis, in patients treated with first generation anti-TNF $\alpha$  therapies and rituximab (Furst *et al.*, 2008). Anti-TNF $\alpha$  therapy can be continued if patients develop psoriasis and respond to conventional yet aggressive treatment of the psoriasis. Induced psoriasis may warrant switching (changing treatment from one TNF inhibitor to another) if lesions are unresponsive to conventional psoriasis treatments. Consider cessation of treatment with an anti-TNF $\alpha$  therapy if skin lesions fail to respond to treatment. (Grade of recommendation C).

### First generation anti-TNF $\alpha$

There have been reports of worsening psoriasis in patients treated with three anti-TNF $\alpha$  therapies (adalimumab, etanercept and infliximab) and rare cases in patients treated with rituximab for RA, SLE and NHL, although it is not clear whether this is related to treatment (Furst *et al.*, 2008) (Grade of recommendation D).

### Abatacept

Evidence to date has not identified any statistically significant skin malignancies, although rashes (including dermatitis) are common.

### Second generation anti-TNF $\alpha$

Evidence is awaited for second generation anti-TNF $\alpha$  therapies and drugs not yet licensed.

## 12. Pregnancy and breastfeeding

All therapies are black triangle drugs (see [www.mhra.gov.uk](http://www.mhra.gov.uk)) and should not be prescribed when patients are trying to conceive a child, during conception or whilst breastfeeding. Patients (of both sexes) should be advised to use effective contraception and, if a pregnancy occurs, this should be reported using the yellow card system, and the patient advised to discuss managing the pregnancy with their prescribing physician. If a pregnancy occurs patients should stop all treatment until reviewed with prescribing physician (Grade of recommendation C). It is also important to ensure the patient discontinues MTX where it is co-prescribed.

Although early evidence should be treated with caution, the initial results are reassuring in relation to the potential threat to the unborn child for those who inadvertently become pregnant whilst being treated with anti-TNF $\alpha$ . Nevertheless, all biologic therapies should still be avoided in those actively seeking to parent a child or for women who are breastfeeding.

Patients treated with rituximab should be advised to use effective contraceptive methods during treatment and for at least 12 months following treatment with rituximab. A 12 month period should elapse after cessation of treatment before breastfeeding.

*Information about contraception:* Family Planning Association ([www.fpa.org.uk](http://www.fpa.org.uk)); Brook clinics ([www.brook.org.uk](http://www.brook.org.uk)).

## 13. Other potential side effects

### Interstitial lung disease/fibrosis

Cases of interstitial lung disease/fibrosis have been reported in patients treated with anti-TNF $\alpha$  therapies. If a patient is suspected of developing ILD or fibrosis, seek medical advice (BSR, 2009). Patients with interstitial lung disease should have their lung function closely monitored if treated with anti-TNF $\alpha$  therapy (Grade of recommendation C).

### Optic neuritis and uveitis

A small number of cases (n=15) of optic neuritis have been reported in patients treated with anti-TNF $\alpha$  therapies. The majority of patients had complete or partial resolution while four patients continued to have symptoms (BSR, 2009).

If uveitis presents whilst on treatment, refer to the prescribing physician and it is likely patients should be changed to another anti-TNF $\alpha$  treatment (BSR, 2009).

### Hepatitis B & C reactivation

There have been reports of reactivation of hepatitis B with chronic carriers of the virus when treated with anti-TNF $\alpha$ . Reports have also been made of worsening hepatitis C following treatment with anti-TNF $\alpha$  therapies. Further studies are required (BSR, 2009) but close monitoring of liver function tests should be undertaken for those treated with anti-TNF $\alpha$  therapies. Refer to guidance produced by NICE ([www.nice.org.uk](http://www.nice.org.uk)) and [www.nhs.uk](http://www.nhs.uk) for further information on risk factors and screening.

### Hepatobiliary events

Features of auto-immune hepatitis have been reported in patients treated with infliximab. Evaluate patients with signs of liver dysfunction before starting treatment and monitor them for signs or symptoms suggestive of liver injury. If there are signs of jaundice or raised ALT (> 5 times upper limit of normal) discontinue and discuss with prescribing physician.

### HIV

Screening for risk factors related to HIV infections should be undertaken before starting treatment with anti-TNF $\alpha$  therapies and tests should be undertaken where risk factors are present. Discuss with prescribing physician before starting treatment.

### Hepato-splenic T cell lymphoma

This has been reported in cases where patients have

been co-prescribed with azathioprine or 6-mercaptopurine for adolescents and young people with CD treated with infliximab or adalimumab (BSR, 2009).

#### **Multifocal Leukoencephalopathy – rituximab**

Multifocal Leukoencephalopathy have been reported in patients treated off license with rituximab for conditions such as SLE.

### **14. Treatment-related reactions**

All protein based therapies carry an increased risk of reactions to the antibody injected or infused. For the current licensed therapies (first generation anti-TNF $\alpha$  therapies, rituximab and abatacept) the development of antibodies to the therapy itself appears to be associated with an increased risk of infusion or injection site reactions and deterioration in treatment efficacy for subsequent infusions therapies for anti-TNF $\alpha$  therapies and rituximab. Injection site reactions to subcutaneous therapies are usually mild and resolve without treatment. Reports of injection site reactions range from 15-36% of those patients receiving subcutaneous biologic injections.

#### **Mild reactions**

Infliximab is reported to have an increased risk of mild to moderate infusion-related reactions when there is a prolonged period before re-treatment.

The most frequently reported infusion-related reactions were mild to moderate ones in patients on abatacept and rituximab. Infusion reactions to abatacept are uncommon (between  $>1/1,000$  to  $<1/100$ ) – the abatacept SPC (2007) states in 2,688 cases there was only one case of anaphylaxis, and other milder infusion related reactions occurred in  $<0.6\%$  of patients. First dose reactions when treated with rituximab occurred in 23-45% of patients in clinical trials treated with rituximab. Patients who were prescribed a pre-treatment regime of glucocorticosteroids were shown to experience significantly reduced acute infusion-related reactions. Reactions decreased following the second infusion to approximately 10-15% of patients (Cohen *et al.*, 2006; DTR, 2008).

#### **Severe reactions**

Anaphylaxis (an immediate, potentially life-threatening reaction to treatment) can potentially occur in all therapies, although to date these are uncommon.

For severe treatment reactions or anaphylaxis, the biologic should be discontinued and treatment

administered immediately according to local trust policy on infusion related reactions and to the drug guidance in the SPC (see algorithm for infusions in Appendix 2).

It is important to manage infusion-related reactions appropriately and to clearly document the severity of the reaction (mild, moderate or severe). For example, depending upon local trust policy, infusion reactions may be managed according to the severity of reaction. For example:

- ◆ mild reaction – decrease rate to 10ml/hr, observations every 10 minutes and gradually increase rate if observations remain satisfactory
- ◆ moderate reaction – withhold treatment for 20-30 minutes. Administer antihistamine and paracetamol. Restart infusion at 10ml/hr increase rate, if observations are satisfactory and patient is asymptomatic
- ◆ severe reaction – stop treatment. Maintain airway and seek urgent medical support and apply local anaphylaxis policy.

For a useful paper that outlines management for infusion reactions, refer to Cheifetz *et al.*, (2003) and *Standards for infusions therapy* (RCN, 2007).

### **15. Limitation and areas of research/debate when assessing treatment benefit**

Although it is clear that MTX in combination with the first generation of anti-TNF $\alpha$  therapy improves response in the majority of patients approximately 30% of patients fail to gain adequate treatment benefit from their first anti-TNF $\alpha$  therapy (Hyrich *et al.*, 2006). For some, changing to an alternative biologic therapy (also known as sequential use or switching) will be an option. However, identifying the best therapeutic option for a specific individual is a complex issue and continues to be an area of intense research. A decision by NICE on sequential use for TNF inhibitors is awaited at time of going to publication.

Some issues for research and debate include:

- ◆ does the rigorous eligibility and treatment response criterion adequately capture the true benefits of treatment?
- ◆ which criteria should be used to assess eligibility and treatment benefit (the DAS 28 has some limitations)? What constitutes a good response to treatment (see Appendix 6, *Eular Response*

*Criteria*)? The DAS 28 may not be an appropriate tool for patients with established or advanced joint disease (and joint damage)

- ◆ is it possible to identify the right treatment for the right patient based on predictable treatment benefits?
- ◆ if a patient fails to benefit from their first TNF inhibitor (based upon treatment response), what is their response likely to be for a subsequent TNF inhibitor? Is this patient's response likely to be different from a patient who develops an adverse reaction to their first TNF inhibitor?
- ◆ patients failing one TNF inhibitor may gain benefit from a subsequent therapy in the same class (switching or sequential use) yet it is difficult to predict treatment response
- ◆ what is the best treatment pathway based upon all biologic therapies and can these predefined or based upon a tailored, individual assessment of potential risks and benefits?

From the practitioner's point of view it is important in assessing patients to take account of factors that may affect treatment benefit. For example:

- ◆ has the patient recently stopped steroid treatment or reduced non-steroidal anti-inflammatory use?
- ◆ have they experienced a recent flare of their disease or had withdrawal of treatment for a period of time pre- or post-surgery?
- ◆ is the timing of the assessment appropriate? This may be particularly relevant if, for instance, a patient receiving an infusion has their assessment for disease activity just before they are due for their next infusion.

For more detailed guidance documents and up-to-date information about biologics and switching, sequential use and next steps in biologic treatment options, refer to NICE ([www.nice.org.uk](http://www.nice.org.uk)) and BSR websites ([www.rheumatology.org.uk](http://www.rheumatology.org.uk)) (BSR, 2009).

### Changing to rituximab

Some units consider a treatment break or 'wash out' period when changing from TNF inhibitors before starting rituximab. There is no specific guidance on this issue although rituximab research studies did specify discontinuation of TNF inhibitors before commencing rituximab (discontinuation of etanercept four weeks prior to treatment, adalimumab and infliximab eight weeks before being treated with rituximab) (Smolen *et al.*, 2007).

Treatment guidelines or protocols locally may be available to guide practitioners but if in doubt, check with the prescribing physician because each individual's risks and benefits in withholding treatment must be considered.

# Section 2: Managing intravenous and subcutaneous biologic therapies

## Preparing to administer intravenous and subcutaneous therapies

This guidance sets out the treatment plan once a biologic therapy has been prescribed by a specialist and the patient has undertaken the full screening process and is eligible for treatment. The patient should have been fully informed about the treatment and provided informed consent (see *Part 2: Children and young people* for specific guidance on paediatric consent).

Once a decision has been made to start treatment with a biologic drug, the patient will be managed by the specialist practitioner who will plan the educational programme with the patient. Where a subcutaneous therapy is to be administered by the patient at home, the patient's general practitioner will be notified in writing and a request will be made for their involvement in the monitoring of the treatment once the patient/carer is trained to administer injections at home. The patient will continue to receive regular follow up regarding their management in the rheumatology clinic.

### Support from pharmaceutical companies

The pharmaceutical companies that manufacture licensed biologic products may sometimes provide extra support to rheumatology units. In some cases, trained nurses are offered to provide support in the preparation and administration of intravenous infusions within the hospital unit. Pharmaceutical companies may also provide home care services for patients using subcutaneous injections, including providing nurses who will train patients on self-administration.

It is important to identify the service options available to support the delivery of drug therapies and provision of additional care in the community. This should be undertaken in collaboration with the medical and management teams in your organisation. In addition, it is essential to clarify that any nursing support provided by pharmaceutical companies will ensure care is given to patients regardless of biologic therapy prescribed. Such external support for patients will usually require endorsement through an internal approval process, depending on your organisation.

## Conditions for administration

### Practitioner competence

Practitioners who are going to administer biologic therapies using intravenous or subcutaneous routes should:

- ◆ be competent in the management of patients receiving injectable medicines
- ◆ have received specific training on the administration of biologic therapies and their side effects
- ◆ be skilled in the administration and management of infusions and have been given education in administering biologic therapies in this way
- ◆ be competent in the education and training of patients in self-administration of subcutaneous injections and disposing of equipment (this training may need to be supported by a local trust protocol or guideline) (see Appendix 4)
- ◆ be competent in resuscitation procedures and have access to full resuscitation equipment
- ◆ have written guidance on the management of anaphylaxis and infusion reactions according to trust policy, and be provided with support by the trust.

For more information see: *Guidance on Standards for Infusion Therapies* (RCN, 2003).

### Delivery setting

In a setting where intravenous or subcutaneous therapies will be administered:

- ◆ a designated specialist rheumatology practitioner should be available on site for advice and to support the administration of the infusions/injections if required
- ◆ preparation of the infusion/injection should be undertaken according to the drug's SPC, and administered within the stipulated time frame

- ◆ full resuscitation facilities and infusion pumps must be readily available.

### Vial sharing

Patients who are to receive intravenous treatments will need to be weighed if the drug dosage has to be calculated according to body weight. In some rheumatology units, following discussion between senior nursing staff, risk management advisers and the pharmacy department, vial sharing is permitted to optimise cost. Local policy and governance procedures need to cover these issues and vial sharing should only be undertaken in a strictly controlled environment. Multi-use vial sharing is not specifically licensed. The National Patient Safety Agency (NPSA) does not support vial sharing and has issued guidance on its use. It is therefore vital that a thorough risk assessment is undertaken and governance processes followed.

See: NPSA *Guidance on the use of vial sharing and competencies for injectable medicines*, at [www.npsa.nhs.uk](http://www.npsa.nhs.uk).

### Pre-infusion/injection assessment

You must fully assess patients before infusion/injection. As well as the assessment set out in *Section 1: Assessing and managing patients*, prior to the infusion you should specifically include:

1. routine questioning of **potential infectious contacts** (such as chicken pox, TB). If you suspect an infection, consult the patient's prescribing physician. Caution: varicella immunity should be checked if an infection is suspected – see local trust or BSR guidance. The patient should confirm that they are not aware of any inter-current infections and that they don't have difficulty in breathing or any shortness of breath
2. women of child-bearing age should confirm the date of their last period and confirm that they are using an effective method of contraceptive. Consider **pregnancy** testing if there is any uncertainty. Re-iterate the risks of a patient receiving these therapies if she could be pregnant
3. patients who are to be treated with abatacept, infliximab, rituximab, or tocilizumab and have had a **previous infusion reaction** should be prescribed an appropriate prophylaxis, referring to your trust's policy or seeking medical advice (see Appendix 2)
4. obtain details of the patient's known **allergies** and review them with the prescribing physician. It is essential that all allergies are taken seriously
5. review the most recent **blood results** prior to treatment.

## Administration and management of intravenous biologic therapies

1. Abatacept
2. Infliximab
3. Rituximab
4. Tocilizumab

This guidance is general only. For additional detail, refer to the SPC (pending publication), discuss with the medical information department of the manufacturer, or discuss with your pharmacist.

### 1. Abatacept

#### Mode of action

Abatacept selectively modulates the activation of T cells involved in the immune system's inflammatory response by blocking co-stimulatory pathways.

#### Licensed indication

Treatment of (moderate to severe) active RA, in combination with MTX in patients who have had an inadequate response or intolerance to DMARDs and at least one anti-TNF $\alpha$  treatment.

#### NICE guidance

NICE has not recommended abatacept for the treatment of RA (NICE TA 141). This is due for review in 2010. You should apply to the PCT via their exceptional circumstance process for funding of treatments outside of NICE guidance.

#### Specific screening

(Refer also to general guidance in Section 1)

- ◆ Viral hepatitis screening.

(See core assessment, screening and monitoring section on page 9)

#### Specific contraindications

- ◆ Hypersensitivity to abatacept or to any of the excipients.
- ◆ Severe and uncontrolled infections.
- ◆ Live vaccines during treatment or within three months of treatment cessation.

(See core assessment, screening and monitoring section on page 9, and Appendix 1)

**Specific cautions**

- ◆ Chronic obstructive pulmonary disease.
- ◆ Patients aged over 75 years, because of increased infection risks.

(See Appendix 1 cautions)

**Treatment regime**

Infusion given at weeks 0, 2, 4 and then every four weeks thereafter.

**Dosage****Medication to be prescribed in the event of infusion-related reaction**

Body weight	Dose	Number of 250mg vials
<60kg	500mg	2
≥60kg to ≤100kg	750mg	3
>100kg	1,000mg	4

Drugs to consider prescribing, for use in the event of an infusion-related reaction:

- ◆ Chlorpheniramine 10 mg IV tds  
(or other appropriate anti-histamine)
- ◆ Hydrocortisone 100 mg IV tds
- ◆ Metoclopramide 10mg IV tds
- ◆ Paracetamol 1g orally qds  
(max 4g in 24 hours)

**Resource considerations****◆ Equipment:**

- a sterile non-pyrogenic, low-protein-binding filter (pore size 0.2µm to <1.2µm) is essential
- a silicone-free disposable syringe is provided with the drug and this must be used to reconstitute each vial
- full resuscitation equipment must be readily available.

**◆ Nursing time:**

- infusions take 30 minutes
- close monitoring required.

**◆ Handling:**

- abatacept does not require any special handling precautions.

**Administration and nursing care**

Refer to workbook, Appendix 1

**◆ Prior to infusion**

1. Check there are no contraindications to treatment as above.
2. Check any recent blood tests are within satisfactory parameters.
3. Record baseline:
  - temperature
  - pulse
  - blood pressure
  - O<sub>2</sub> saturation levels if indicated.
4. Urinalysis – MSU if infection suspected and consider if infusion should be administered.

**◆ Preparation of infusion**

Prepare the infusion according to manufacturer's guidelines. Abatacept is supplied in 250mg vials as a dry powder. Each vial is reconstituted with 10mls of sterile water for injection using the silicone-free disposable syringe provided with each vial and an 18-21 gauge needle.

**◆ Administering the infusion**

Abatacept is infused through a filter (see equipment) into a peripheral cannula using an IV pump with a primed line (0.9% sodium chloride).

Abatacept should be administered over 30 minutes.

**◆ Clinical observations during infusions**

No routine observations during the infusion are required, however in the event that the patient reports feeling unwell, observations should be taken.

Observe for any signs of respiratory deterioration in those with COPD.

Observe for side effects throughout: take appropriate action as shown below and record any adverse events in the patient's notes.

**Infusion reactions and adverse events**

Anaphylactic reactions have been reported (although uncommon). Should this occur:

1. stop the infusion
2. call the doctor
3. administer intravenous hydrocortisone, intravenous chlorpheniramine (or other appropriate

antihistamine) and/or any emergency treatment as prescribed and according to local policy on managing anaphylactic reactions.

Acute infusion-related events (i.e. those that occur within one hour of the infusion) are most commonly headache and nausea ( $\geq 1/10$  patients). Dizziness and hypertension may also occur. Seek medical advice in the case of hypertension.

For full list of adverse effects, see the drug's SPC, available at: [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk).

### Post-infusion care and advice to patients

Discharge the patient after the infusion, providing observations taken one hour after the infusion start time are satisfactory.

Before the patient leaves:

1. advise them to seek medical advice if they develop any symptoms which suggest an infection (e.g. fever in the hours or days after the infusion). Provide contact numbers for the rheumatology department or first contact point e.g. GP and/or attendance at the hospital's accident and emergency department (A&E)
2. make sure regular MTX monitoring, according to BSR/BHPR and local guidelines is set up
3. make patients who have diabetes aware that they may experience a falsely elevated blood glucose reading on the day of the infusion, as abatacept interferes with blood glucose monitoring strips (glucose dehydrogenase pyrroloquinolinequinone GDH-PHQ)
4. ensure follow-up for assessment or next infusion has been arranged
5. ensure they have a Biologics Alert Card to carry with them ([www.arc.org.uk](http://www.arc.org.uk)).

## 2. Infliximab

### Mode of action

Infliximab is a monoclonal antibody biologically engineered using part human and part mouse antibodies and targets the cytokine TNF alpha.

### Licensed indication

It is licensed for use in RA, AS, PsA, psoriasis, ulcerative colitis and paediatric Crohn's and adult CD.

### NICE guidance

**RA:** TA130 (Oct 2007) infliximab is approved for the treatment of active RA in patients who have already tried MTX and another DMARD

**AS:** TA143 (May 2008) infliximab is not approved for people with AS

**PsA:** TA104 (July 2007) infliximab can be offered as an option for treating adults with PsA if:

- ◆ etanercept causes a reaction which means that the patient should not continue taking it, or
- ◆ the patient has a condition or is taking another medicine that means they should not take etanercept, or
- ◆ the patient has major difficulty injecting themselves *and* the patient meets the following criteria:
  - arthritis with three or more tender joints and three or more swollen joints
  - at least two other DMARDs, given on their own or together, have not worked.

*This guidance is due to be updated by NICE in September 2009.*

### Specific screening

*(None, but see core assessment, screening and monitoring section on pages 9-19)*

### Specific contraindications

- ◆ Hypersensitivity to infliximab or other murine proteins

*(See core assessment, screening and monitoring section on pages 9-19)*

### Treatment regime

#### RA

Infusions at weeks 0, 2, 6 and then every eight weeks. Initial dose 3mg per kg body weight.

#### PsA

Infusions at weeks 0, 2, 6 and then every eight weeks. Initial dose 5mg per kg body weight.

#### AS

Infusions at weeks 0, 2, 6 and then every six to eight weeks. Initial dose 5mg per kg body weight.

### All indications

If there has been inadequate response, the dose or frequency of injections may be increased (see SPC).

Weekly MTX should be co-prescribed according to the indication see SPC for details. See page 22 for advice on vial sharing.

### Medication to be prescribed in the event of an infusion-related reaction

Drugs to consider prescribing, for use in the event of an infusion-related reaction:

- ◆ Chlorpheniramine 10 mg IV tds  
(or other appropriate antihistamine)
- ◆ Hydrocortisone 100 mg IV tds
- ◆ Metoclopramide 10mg IV tds
- ◆ Paracetamol 1g orally qds  
(max 4g in 24 hours)

### Resource considerations

#### ◆ Equipment:

- a sterile low protein binding filter (pore size < 1.2µm) is essential
- full resuscitation equipment must be readily available.

#### ◆ Nursing time:

- infusions take between 1-2 hours
- close monitoring required
- patient will need to be observed for 2 hours following first 4 infusions, and then for 1 hour following subsequent infusions.

#### ◆ Handling:

- infliximab does not require any special handling precautions.

### Administration and nursing care

#### ◆ Prior to infusion

1. Check that there are no contraindications to treatment.
2. Check any recent blood tests are within satisfactory parameters.
3. Record baseline:
  - temperature
  - pulse
  - blood pressure
  - O<sub>2</sub> saturation levels if indicated.
4. Urinalysis – MSU if infection is suspected and consider whether infusion should be administered.

#### ◆ Preparation of infusion

This should be done in accordance with the manufacturer's guidelines (available on the package insert or downloaded from [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk)).

(See also *Limitations and areas of research/debate when assessing treatment benefit* on page 19)

#### ◆ Administering the infusion

Infliximab is infused through a filter (see *Equipment*) into a peripheral cannula using an IV pump with a primed line. It should be infused over a period of 1-2 hours (see SPC).

In carefully selected patients who have tolerated three initial two hour infusions of standard dose infliximab (3mg/kg), consideration can be given to subsequent infusions being administered over no less than an hour (Schering Plough, Remicade SPC, 2008).

#### ◆ Clinical observations during infusions

Every 30 minutes, temperature, pulse and blood pressure should be recorded.

Observe for side effects throughout, taking appropriate action as shown below. Record any adverse events in the patient's notes.

For full list of adverse effects, please see drug specific SPC at: [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk).

### Post-infusion care and advice to patients

Infusion reaction	Action
Mild fever, chills, pruritus.	Slow down rate of infusion.
Chest pain, hypertension, hypotension and/or dyspnoea.	Stop infusion. Alert physician – consider use of IV hydrocortisone and/or IV chlorpheniramine (antihistamine – if prescribed or otherwise pre-authorised by local policy/PGD). Review with physician – consider restarting infusion after 20 minutes at a slower rate.
Anaphylactic reaction.	Stop infusion. Call physician. Administer IV hydrocortisone IV Chlorpheniramine (antihistamine) and any emergency treatment as indicated. If prescribed or pre-authorised.

Monitor blood pressure, temperature and pulse every 30 minutes for two hours following first four infusions, and then for one hour following subsequent infusions.

Discharge patient after the appropriate time, providing all observations are satisfactory.

Before the patient leaves:

1. advise them to seek medical advice if they develop any symptoms which suggest an infection (e.g. fever in the hours or days after the infusion). Provide contact numbers for the rheumatology department or first contact point e.g. GP and/or attendance at the hospital's A&E
2. make sure regular MTX monitoring, according to BSR/BHPR and local guidelines, is set up where appropriate
3. ensure follow-up for assessment or next infusion has been arranged
4. ensure they have a Biologics Alert Card to carry with them ([www.arc.org.uk](http://www.arc.org.uk)).

### 3. Rituximab

#### Mode of action

Rituximab is a genetically engineered chimeric mouse/human antibody designed to deplete pre-cursor B cells.

#### Licensed indication

It is licensed for use in severe active RA in combination with MTX in adult patients who have had an inadequate response or intolerance to other DMARDs, including one or more TNF inhibitor therapies.

#### NICE guidance

NICE has approved the use of rituximab in patients who have had an inadequate response to or intolerance of other DMARDs, including at least one anti-TNF $\alpha$  treatment (TA 126 2007).

#### Specific screening

- ◆ Hepatitis B screen.
- ◆ Immunoglobulin levels.
- ◆ CD19 may be considered.

(See also *general screening for biologics, pages 9 to 19*)

Specific contraindications

- ◆ Hypersensitivity to rituximab or other murine proteins.
- ◆ Use in children (safety not yet established).

(See *general contraindications for biologics, pages 9 to 19*)

#### Specific caution

- ◆ Any inactivated vaccinations should be given one month prior or at least seven months after treatment. No live vaccines should be administered.

#### Treatment regime

A course includes two infusions given on day 0 and day 14. Further courses may be considered 6-12 months after initial course if adequate response is achieved (DAS 28 improvement of 1.2 points or more).

#### Dosage

- ◆ IV 1000mg rituximab on day 0 and day 14.
- ◆ MTX weekly.

#### Drugs prior to infusion

- ◆ Methylprednisolone 100mg IV (100mgs in 100mls normal saline infused over 30 minutes).

(The methylprednisolone should be given 60 minutes before rituximab).

- ◆ Paracetamol 1G orally (30 mins prior to infusion)
- ◆ Chlorpheniramine 10 mg IV (30 mins prior to infusion) or an oral anti-histamine according to local protocol.

#### Medication to be prescribed in the event of an infusion-related reaction

Additional drugs to be prescribed, for use in the event of an infusion-related reaction:

- ◆ Chlorpheniramine 10 mg IV tds (or other appropriate anti-histamine)
- ◆ Hydrocortisone 100 mg IV tds
- ◆ Metoclopramide 10mg IV tds
- ◆ Paracetamol 1g orally qds (max 4g in 24 hours/ minimum 4 hours apart)

#### Resource considerations

- No specific resources required
- ◆ **Equipment:**
  - full resuscitation facilities
  - infusion pump required.
- ◆ **Nursing time:**
  - first infusion may take between 6-7 hours
  - second infusion can be completed more quickly if no adverse effects during first infusion
  - close monitoring required.

◆ **Handling:**

- rituximab is not an irritant. There are no special handling precautions in the case of extravasations.

**Administration and nursing care**

◆ **Prior to infusion**

1. Check that there are no contraindications to treatment as above.
2. Check no analgesics containing Paracetamol have been taken within last 4 hours.
3. Check any morning dose of anti-hypertensives have been omitted.
4. Check any recent blood tests are within satisfactory parameters.
5. Record baseline observations of:
  - temperature
  - pulse
  - blood pressure
  - O<sub>2</sub> saturation levels (if indicated).
6. Urinalysis – MSU if infection suspected and consider if infusion should be administered.
7. Administer pre-infusion medications as above.

◆ **Preparation of infusion**

In units where staff prepare the infusions, make up rituximab according to manufacturer’s guidelines.

◆ **Administering the infusion**

Rituximab is infused through a peripheral cannula using an IV pump with a primed line.

The following regime is based on a concentration of 2mgs/ml i.e. 1,000mgs in 500mls. (Rituximab can be diluted to a concentration of between 1-4mgs/ml normal saline).

The rate of the infusion will depend on the concentration of the rituximab and whether it is the first or second infusion. In the event of a reaction to the first, the second infusion should be administered as per instructions for the first infusion.

**Infusion rate for day 0**

Time	mgs/hour	mls/hour
1st 30 minutes	50mg/hour	25mls/hour
2nd 30 minutes	100mg/hour	50mls/hour
Then the rate can be increased by 50mg/hour (25mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur.		

**Infusion rate for day 14 if the patient had no reaction to the first infusion**

Time	mgs/hour	mls/hour
1st 30 minutes	100mg/hour	50mls/hour
2nd 30 minutes	200mg/hour	100mls/hour
Then the rate can be increased by 100mg/hour (50mls/hour) every 30 minutes to a maximum rate of 400mg/hour (200mls/hour) providing no adverse reactions occur.		

Concentration	1mg/ml	2mgs/ml	4mgs/ml
Volume of fluid	1,000mls	500mls	250mls

◆ **Clinical observations during infusions**

1st hour every 15 minutes then every 30 minutes.

(Prior to increasing the rate of infusion and until infusion completed).

- Blood pressure.
- Pulse.
- Temperature.
- O<sub>2</sub> saturation levels (if indicated).

Note: Most reactions have been noted during the first few minutes of the infusion, so observe the patient carefully during this time and following each increase in infusion rate.

**Infusion reactions and adverse events**

Acute infusion reactions may occur within 1-2 hours of the first rituximab infusion. These may include:

- ◆ fever
- ◆ headache
- ◆ rigors
- ◆ flushing
- ◆ nausea
- ◆ rash
- ◆ upper respiratory tract infections (URTI) symptoms.

Transient hypotension and bronchospasm are usually related to the infusion rate. A small increase in serious infections has been noted (but not opportunistic infections such as TB).

**Post-infusion care and advice to patients**

Discharge patient once infusion is complete and observations satisfactory.

Infusion reaction	Action
Mild to moderate reactions (30-35% at 1st infusion; less with the 2nd (see above)). e.g. low grade fever; hypotension <30mmHg from baseline.	Halve the infusion rate. Consider giving prn medication.
Moderate to severe reactions (uncommon: frequency is reduced by the concomitant use of IV steroids). e.g. fever >38.5°C; chills; mucosal swelling; shortness of breath; hypotension by >30mmHg from baseline.	STOP the infusion and treat the symptoms. Contact the doctor. The infusion should be restarted at half the previous rate only when the symptoms have resolved.

Before the patient leaves:

1. advise them to seek medical advice if they develop any symptoms which suggest an infection (e.g. fever in the hours or days after the infusion). Provide contact numbers for the rheumatology department or first contact point e.g. GP and/or attendance at the hospital's A&E
2. make sure regular MTX monitoring, according to BSR/BHPR and local guidelines, is set up where appropriate
3. ensure follow-up for assessment or next infusion has been arranged
4. ensure they have a Biologics Alert Card to carry with them ([www.arc.org.uk](http://www.arc.org.uk)).

## 4. Tocilizumab

### Mode of action

IL-6 is pro inflammatory cytokine produced by a number of cells including T and B cells. Tocilizumab is an IL-6 receptor inhibitor and binds to soluble and membrane bound IL-6 receptors inhibiting the inflammatory response.

### NICE guidance

Single Technology Appraisal – due in the final quarter, 2009.

### Specific screening

(See general screening for biologics, page 9)

- ◆ Caution in treating patients with consistent low neutrophils or platelet count (ANC < 2 x 10<sup>9</sup>/l) or platelet count below 100 x 10<sup>3</sup> /µl.

- ◆ Blood tests before each infusion. Withholding treatment or dose reductions may be indicated if results are abnormal.

Discuss with prescribing physician if:

- ◆ absolute neutrophils count (ANC) < 0.5
- ◆ platelets < 50
- ◆ LFT > 3 x 5 upper limit of normal repeat blood test and if remain raised discuss with prescribing physician
- ◆ raised lipid profiles as treatment with lipid lowering agents may be required.

### Specific contraindications

*These are suggested, pending publication of the SPC.*

- ◆ Check neutrophils prior to treatment. ANC < 2 x 10<sup>9</sup>/l. Depending upon the level of neutropenia, treatment may need to be withheld or discontinued.
- ◆ It may be necessary to withhold or stop treatment if ALT/AST > 3-5 times upper limit of normal or greater. Confirm results by repeating tests and discuss with prescribing physician.

(See also general contraindications for biologics, page 9)

- ◆ A drop in platelets < 100 x 10<sup>3</sup> /µl may require interruption of treatment if < 50 x 10<sup>3</sup> /l.

### Treatment regime

#### RA

Infusions every four weeks.

#### Dosage

Initial dose 8mg/kg of body weight.

Weekly MTX should be co-prescribed according to the indication (see SPC for details).

### In the event of an infusion-related reaction

Drugs to consider prescribing, for use in the event of an infusion-related reaction:

- ◆ Chlorpheniramine 10 mg IV tds  
(or other appropriate anti-histamine)
- ◆ Hydrocortisone 100 mg IV tds
- ◆ Metoclopramide 10mg IV tds
- ◆ Paracetamol 1g orally qds  
(max 4g in 24 hours)

### Resource considerations

#### ◆ Equipment:

- full resuscitation equipment must be readily available.

#### ◆ Nursing time:

- infusions over one hour
- close monitoring required.

#### ◆ Handling:

- tocilizumab must be diluted in a controlled environment using an aseptic technique.

### Administration and nursing care

This is preliminary guidance – practitioners should refer to the SPC when this therapy is licensed.

#### ◆ Prior to infusion

1. Check that there are no contraindications to treatment as above.
2. Check any recent blood tests are within satisfactory parameters.
3. Record baseline:
  - temperature
  - pulse
  - blood pressure
  - O<sub>2</sub> saturation levels (if indicated).
4. Urinalysis – MSU if infection is suspected and consider whether infusion should be administered.

#### ◆ Preparation of infusion

This should be undertaken in accordance with the manufacturer's guidelines. Tocilizumab is supplied in vials and requires reconstitution and administration from a 100ml infusion bag according to the SPC and manufacturer's instructions. See handling above.

#### ◆ Administering the infusion

Tocilizumab is infused through a peripheral cannula using an IV pump with a primed line. It should be infused over a period of one hour (refer to the SPC).

Anaphylactic reactions and sensitivity reactions have been reported. The development of antibodies to tocilizumab may increase sensitivity reactions.

#### ◆ Clinical observations during infusions

Every 30 minutes, temperature, pulse and blood pressure, should be recorded.

Observe for side effects throughout, taking appropriate action as shown below record any adverse events in the patient's notes.

### Infusion reactions and adverse events

Infusion reaction	Action
Mild fever, chills, pruritus.	Slow down rate of infusion.
Chest pain, hypertension, hypotension and/or dyspnoea.	Stop infusion. Alert physician-consider use of IV hydrocortisone and /or IV chlorpheniramine (or other chosen antihistamine).  Review with physician – consider restarting infusion after 20 minutes at a slower rate.
Anaphylactic reaction.	Stop infusion. Call physician. Administer IV hydrocortisone IV chlorpheniramine (antihistamine) and any emergency treatment as indicated.

For full list of adverse effects, please see tocilizumab SPC when licensed at: [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk).

### Post-infusion care and advice to patients

Monitor blood pressure, temperature and pulse post infusion. Confirm further management and monitoring post infusion with SPC when licensed.

Discharge patient after the appropriate time, providing all observations are satisfactory.

Before the patient leaves:

1. advise them to seek medical advice if they develop any symptoms which suggest an infection (e.g. fever in the hours or days after the infusion). Provide contact numbers for the rheumatology department or first contact point e.g. GP and/or attendance at the hospital's A&E
2. make sure regular MTX monitoring, according to BSR/BHPR and local guidelines, is set up
3. ensure follow-up for assessment or next infusion has been arranged
4. ensure they have a Biologics Alert Card to carry with them ([www.arc.org.uk](http://www.arc.org.uk)).

## Administration and management of subcutaneous biologic therapies

### Therapies delivered subcutaneously

Biologic therapies administered via the subcutaneous route include:

- ◆ adalimumab
- ◆ anakinra
- ◆ etanercept
- ◆ certolizumab pegol
- ◆ golimumab.

*For detailed treatment criteria, screening and assessment procedures, refer to Section 1, page 9.*

### Adalimumab

Adalimumab is a human monoclonal antibody to TNF $\alpha$ . It binds to and neutralises TNF alpha, inhibiting its action. Dose for all indications is 40mg every other week.

Indications include:

- ◆ **AS.** Severe active AS with inadequate response to conventional therapy (poor symptom relief from two non-steroidal anti-inflammatories)
- ◆ **Psoriasis.** Plaque psoriasis defined by PASI of 10 or more and a dermatology life quality index (DLQI) score greater than 10. Failure to respond to standard systemic therapy and psoralen and long wave ultraviolet radiation/or intolerant/contraindication to these treatments
- ◆ **PsA.** Active and progressive PsA with inadequate response to previous DMARD therapy.
- ◆ **RA.** 40mg every other week or 40mg weekly monotherapy or in combination with MTX. (Adalimumab 40mg once a week monotherapy has not been recommended by NICE but if indicated, you must make an exceptional case request)
- ◆ **CD.** Refer to SPC.

Adalimumab is also licensed for the treatment of children and young people (see part 2: children and young people JIA on page 35).

### Anakinra

Anakinra is a recombinant form of the human interleukin-1 receptor antagonist (IL-1RA). IL-1RA is an anti-inflammatory cytokine. Anakinra actively competes with IL1 (a pro-inflammatory cytokine) in activating an inflammatory response.

Licensed dose 100mg once a day in combination with MTX. Anakinra is not recommended by NICE (2003).

### Etanercept

Etanercept is a soluble fusion protein that inhibits the normal action of TNF receptors by blocking TNF alpha.

Licensed dose 50mg once weekly or 25mg twice weekly

either as a monotherapy (for those intolerant to MTX) or in combination with MTX.

Indications include:

- ◆ **AS.** Severe active AS with inadequate response to conventional therapy (poor symptom relief from two non-steroidal anti inflammatories)
- ◆ **Psoriasis.** Plaque psoriasis defined by PASI of 10 or more and a DLQI score greater than 10. Failure to respond to standard systemic therapy and psoralen and long wave ultraviolet radiation/or intolerant/contraindication to these treatments
- ◆ **PsA.** Active and progressive PsA (three or more tender and three or more swollen joints) with inadequate response to previous DMARD therapy
- ◆ **RA.** Moderate to severe RA. 25mgs twice weekly or 50 mgs weekly in combination with MTX. Can be administered as a monotherapy in case of intolerance or where deemed inappropriate.

Etanercept is also indicated for children and young people. (See also Part 2: Children and young people, for juvenile idiopathic arthritis.)

**Note:** NICE guidance for the management of RA (pending publication 2009) provides guidance for the use of etanercept, adalimumab and infliximab in adults with RA.

### Certolizumab pegol

*This therapy is pending license in 2009*

Certolizumab pegol is a pegylated (hydrated) human fab fragment of IgG1 monoclonal antibody against TNF alpha with reported enhanced bioavailability (serum half life of approximately 14 days).

**Note:** Licence pending for the treatment of RA in 2009 and will be subject to review by NICE. If a license is granted for certolizumab pegol, refer to the SPC for details and seek further guidance from your pharmacist.

### Golimumab

*This therapy is pending license in 2009*

Golimumab is a fully human monoclonal antibody inhibiting TNF $\alpha$ . Marketing authorisation is pending for AS, PsA and RA.

**Note:** Licence pending for the treatment of RA in 2009 and will be subject to review by NICE. If a license is granted for golimumab refer to the SPC for details and seek further guidance from your pharmacist.

## Delivery of subcutaneous therapies to patients' homes

Once a patient has been assessed and fulfils the criteria for treatment with subcutaneous biologic therapy, a prescription should be completed to enable the patient to receive their first treatment to their home. The practitioner who prescribes the biologic therapy must be competent in managing this patient group and have a sound knowledge of the medication being prescribed. The signing of the prescription is the first step in authorising home delivery of the subcutaneous biologic therapies.

Some rheumatology units are able, as part of their specialist service, to train patients to self administer their treatment and arrange home deliveries once the patient is competent to self administer.

Pharmaceutical companies provide home care services for patients using subcutaneous injections. Treatments are delivered directly to the patient's home and reduce the overall cost of purchasing the drug (VAT exempt). Nurses employed by an independent organisations but funded by the cost of the drug are available as part of the service to deliver subcutaneous therapies to the patient in their own home and train patients in self administration. These services will also arrange regular delivery of their treatment and collect clinical waste. Patient information literature, training videos and alert cards are also provided.

A training and competency package checklist is used to assess the patients' ability to self inject.

In many cases however, and depending upon local provision, patients may elect to be trained to self administer their subcutaneous biologic therapy supported by their usual team from the rheumatology department.

There are also a number of patient organisations and websites that the patient can access for additional support (see Appendix 13).

## Ongoing management for all biologic therapies

### Patient advice

It is important to provide patients with the information they require to be informed and effectively self-manage their condition before their next appointment or treatment.

Provide information on:

- ◆ the **date and time** of their next

appointment/treatment. The next appointment/treatment should follow according to stipulated assessment timeframes (16 weeks for rituximab or six months for anti-TNF $\alpha$  therapies). The patient should be aware of the assessment criteria

- ◆ the **blood tests/investigations** required before the next appointment – when and where these should be taken, and how the results will be recorded (for example, in the patient shared care monitoring booklet)
- ◆ what the patient should look out for when **monitoring** themselves and their response to treatment. For example:
  - report any infections promptly
  - new symptoms suggestive of infection or drug reaction (for example dry cough, sore throat, bruising and rashes)
  - any changes in risks related to pregnancy or fathering a child (they should advise the team promptly so that guidance on management can be provided)
  - what to do if they observe any side effects.
- ◆ **contact details** for the service, including out-of-hours contact numbers, using either the on-call GP service or on-call rheumatologist
- ◆ the Arthritis Research Campaign (arc) **Biologics Alert Card** [www.arc.org.uk](http://www.arc.org.uk). Explain why they should show this to anyone they see who is providing any form of treatment to them (for example dentists, chiropractors, doctors or nurses they see for another condition). Encourage them to carry this card with them at all times
- ◆ the fact that you will be writing to their GP about their treatment. Where appropriate the GP will also be informed if information has been submitted to the BSRBR.

### Monitoring points

You should:

- ◆ seek medical advice from prescribing physician if, at review, there are any indicators that suggest there may be abnormalities, infections or reactions in the patient, or if you have any doubts about whether to continue the treatment
- ◆ be aware of any potential adverse reactions to treatment including trends or sudden changes in the blood picture, or symptoms such as sore throat or other signs suggestive of blood dyscrasia

- ◆ observe for any signs of infections, rashes or lupus-like syndrome. If present, repeat blood tests for anti-dsDNA. If the tests are positive, review them with the prescribing physician
- ◆ ensure that the patient is coping and has adequate support, from a psychological and social perspective, with their treatment regimes and monitoring plans.

### Yellow card reporting

Nurses and practitioners must report any potential drug side effects or suspected adverse drug reactions to a medication, using the yellow card reporting system. See [www.mhra.gov.uk](http://www.mhra.gov.uk) for yellow card reporting or use the pages at the back of the British National Formulary.

### Unplanned care issues

This section will help guide you on some of the common issues and enquiries which patients may seek advice about while they are on biologic therapies. The following scenarios have been identified from routine telephone advice-line calls.

**Question:** Patient complains of a **sore throat**.

- ◆ Observe for warning signs that might indicate a systemic infection (exudate on lymph nodes, extreme tenderness or swelling or fever) or immunosuppression (neutropenia/rash). Withhold biologic and DMARD, request immediate FBC and seek medical advice.

#### Advice

- ◆ If no signs indicative of systemic disease or immunosuppression, reassure the patient and advise them to take paracetamol and plenty of fluids to reduce their temperature. Encourage them to seek further guidance if symptoms do not resolve or their condition deteriorates. They should recommence treatment once any minor infections are resolved.

**Question:** Patient is concerned as they are experiencing **breathlessness**.

- ◆ Take a detailed medical history, including when symptoms started and whether they were of sudden or gradual onset. Consider other long standing comorbidities (e.g. respiratory or cardiac conditions).
- ◆ Is the breathlessness accompanied by classic signs of a cold or productive of sputum (indicating possible respiratory infection).
- ◆ Exclude cardiac causes – ask if they have any associated chest pain?
- ◆ Current medications – some medications, particularly MTX, can cause pneumonitis.

#### Advice

- ◆ Advise the patient to seek an urgent medical opinion or seek guidance from the prescribing physician.
- ◆ Advise the patient to withhold MTX and/or biologic therapy until they have been seen and pneumonitis or a respiratory infection have been excluded.

**Question:** Patient is thinking about **planning a family** or is worried they may have **conceived** whilst on treatment.

#### Advice

- ◆ If the patient wants to plan a family and is on a biologic therapy, arrange for a prompt appointment with prescribing physician or specialist team to outline treatment options. Advise the patient that they need to allow at least three months clear of treatment (particularly with MTX) before they can conceive. Although currently outside guidance of the SPC for some biologics, where evidence is greater it may be they can continue on their biologic providing the consultant and patient discuss the risks and benefits of such decisions, which need to balance the potential risks to the unborn child against the risks to the patient of stopping treatment.
- ◆ If there is a possibility that there is an unplanned pregnancy, arrange an urgent pregnancy test. Stop treatment with biologics or disease modifying drug therapies. The patient will require an urgent referral to specialist obstetrician and specialist rheumatology support to discuss concerns and next steps in management.
- ◆ If a pregnancy is confirmed, report to the MHRA using the Yellow Card Reporting System and inform the BSRBR. You may also choose to inform the medical information department of the drug's manufacturer (contact details in the back of the BNF).

**Note:** Biologic therapies are relatively new therapies and in the majority of cases remain black triangle drugs and should not be prescribed to those wishing to conceive. In addition co-prescribed drugs such as MTX are potentially harmful to the unborn child. Some drugs may also reduce fertility. Breastfeeding should not be undertaken whilst on black triangle therapies such as biologic therapies.

**Question:** The patient is to visit the **dentist** for a tooth extraction.

#### Advice

- ◆ Advise the patient to take their arc Biologic Alert Card and ensure the dentist has an opportunity to see this card before any treatment is planned.

## 2 Children and young people

### Introduction

Part 2 provides guidance for paediatric rheumatology clinical nurse specialists caring for children and young people of 18 years and younger who are receiving biologic therapies for JIA. The role of paediatric rheumatology nurses is pivotal in ensuring that children, young people and their families and carers are fully informed about the biologic therapy that the young person is receiving.

At the time of the 2003 Royal College of Nursing biologics guidance document, only etanercept was licensed for use in children and young people, but now adalimumab (marketed as Humira) is also licensed (although the licence is restricted to young people aged 13-17 years). Here we focus on these two therapies, but recognise that other biologic therapies are also used in paediatric practice although used as unlicensed indications.

Children and young people with JIA are significantly fewer than the number of adults with RA. About 10,000 children in the UK are affected (NICE, 2002). JIA is relatively rare, with an estimated incidence in the UK of 1:10,000 children, which equates to 1,000 new cases per year. For classification of JIA, see Appendix 8.

### This guidance

The guidance in Part 2 aims to provide a standardised approach to the care children and young people require when receiving biologic therapies. The experience gained in the assessment and management of children and young people receiving these drugs provides an opportunity for paediatric rheumatology clinical nurse specialists and paediatric rheumatologists to develop a framework for practice and a consensus on management.

These revised guidelines have been developed in collaboration with the RCN Rheumatology Forum Steering Committee Working Party, and in conjunction with other members of the Arthritis Musculoskeletal Alliance (ARMA). You will find specific references in Part 2 of the *References* section, specific resources under *Websites and resources*, and additional guidance on treating children and young people in Appendix 8 (JIA), Appendix 9 (BSPAR guidance) and Appendix 10 (varicella antibodies).

The RCN Working Party identified four key national issues in the care of children and young people with JIA:

1. nursing resource implications for biologic therapies: no additional funding has been associated with the endorsement of such therapies and the associated requirements, namely the implementation of the British Society of Paediatric and Adolescent Rheumatology (BSPAR) Biologics and New Drugs Register (BNDR) as mandated in the NICE guidelines for etanercept
2. the continued need to provide guidance on specific clinical issues in the assessment and management of children and young people receiving biologic therapies
3. the continued need for consensus and clarity about emerging evidence and about what can be agreed as best practice
4. the national service frameworks highlighting the specific needs of children and young people – the NSF (2004) England and Wales, and Specialist Children's Services Framework in Scotland.

Note that in preparing this guidance, the Working Party found that in some areas of clinical practice, the evidence to support best practice remains unclear. In this instance, evidence is provided in a pragmatic way by clinicians experienced in the assessment and management of children and young people receiving biologic therapies.

*Royal College of Nursing Paediatric Rheumatology Nurses Group*

*Royal College of Nursing Children and Young People's Field of Practice*

# Section 1: Assessing and managing children and young people needing biologic therapies

## The special needs of children and young people

As a specialist practitioner, it is essential that you are aware that the care of children and young people of 18 years and younger with JIA should be managed according to the BSPAR *Standards of Care* (2009) and the Department of Health (2004) NSF in England and Wales and Specialist Children's Services Framework in Scotland.

Children and young people should be admitted to designated areas in hospital which meet their specific needs. The Department of Health in England has highlighted the specific needs of adolescents and the need for effective transition from children's to adult services DH (2004) and RCN (2003). In the event that there is a lack of adolescent facilities, a young person could choose to be admitted to either a children's or an adult ward. Acute health care providers must ensure that the needs of young people are met in appropriate environments by appropriately trained personnel. Children and young people with JIA require prompt diagnosis and referral to specialist paediatric rheumatology multi-disciplinary team.

Around the UK, there are many centres with specialist paediatric rheumatology teams. They often work in clinical networks with doctors (paediatricians, adult rheumatologists and GPs), nurses (in hospitals and in the community), therapists (physiotherapists and occupational therapists) and other health care professionals. All these professionals aim to provide high quality clinical care nearer to the child's home and minimise disruption for the family. They also work with schools and social services to support the child and family in the community and throughout the child's education (BSPAR, 2009).

## Treating JIA with biologic therapies

In March 2002, NICE published guidance on anti-TNF $\alpha$  treatment etanercept for children and young people

with JIA aged 4-17 years. In September 2008 adalimumab was also licensed for young people aged 13-17 years who have active polyarticular JIA, in combination with MTX. Adalimumab can be given as a monotherapy in a case of intolerance to MTX, or when continued treatment with MTX is inappropriate.

It is important to acknowledge that in practice, many JIA patients in the UK under the age of 18 are being given other biologic therapies such as abatacept, anakinra, infliximab, rituximab and tocilizumab all of which, are currently used as unlicensed indications. This guidance does not provide specific advice in respect of these, but considers it is essential that all children and young people receiving biologic therapies have their care managed by a tertiary paediatric rheumatology service, and these, in turn, may share care with the child or young person's local hospital. Information about accessing tertiary paediatric rheumatology services is available at [www.bspar.org.uk](http://www.bspar.org.uk).

## The need for paediatric rheumatology clinical nurse specialists

Whilst there has been some expansion in the numbers of paediatric rheumatology clinical nurse specialists, there still remains a significant number of children and young people who do not have exclusive access to such professionals. Care may be shared with other health professionals, including adult rheumatology nurse specialists, community children's nurses, children's nurses, adult rheumatology nurses and allied health professionals. A non-registered children's nurse currently providing care to children and young people must only do so under the direct supervision of a registered children's nurse and practice only within their level of competency (NMC, 1997, NMC, 2007, NMC, 2008).

The Royal College of Nursing calls for an expansion in the number and role of paediatric rheumatology clinical nurse specialists, acknowledging that in practice, focused, specialised care for children and young people

is only achievable through the provision of shared care arrangements. Paediatric clinical nurse specialists facilitate care through the education and training of nurses, particularly local community children's nursing teams and children's nurses in the child's/ young person's local health care facility.

## The Biologics Register

The children and young person's register is managed by the BSPAR ([www.bspar.org.uk](http://www.bspar.org.uk)). The BSPAR's BNDR is currently only collecting data about patients with JIA who are receiving etanercept; comparison data is also being collected from patients receiving MTX. Tertiary centres may, however, independently and without formal requirement collect data in a similar format about patients receiving other biologic therapies who are not under the remit of NICE guidance.

Further information is available by contacting the BNDR co-ordinator at [www.bspar.org.uk](http://www.bspar.org.uk) (see contact section).

## Special skills for working with children and young people receiving biologic therapies

Paediatric rheumatology clinical nurse specialists and registered children's nurses who assist in the administration of biologic therapies should work within an appropriate multi-disciplinary team and:

- ◆ have specialist expertise in the biologic therapies they are administering and be fully aware of the potential side effects of treatment and of monitoring schedules
- ◆ be skilled in teaching children and young people about their treatment, recognising their patient's level of physical and cognitive abilities
- ◆ be competent in the administration of subcutaneous injections and have the ability to teach and assess the competence of children, young people and their families/carers in such techniques. When learning these techniques, children and young people need time to play and explore placebo equipment and time to practice the techniques under the supervision of the specialist nurse or delegated colleagues, until both the family and the nurse feel they are safe and competent
- ◆ involve other specialists such as hospital play

specialists who can be invaluable in supporting children and young people who require injections, particularly those who are needle phobic.

## Assessing and managing patients

### 1. Selecting patients for treatment

*For eligibility criteria for treatment with etanercept in children and young people, see Appendix 9.*

To ensure that children and young people under 18 years old are selected appropriately to receive biologic therapies, you should undertake a risk benefit analysis of each patient which is based on:

1. fulfilment of the BSPAR eligibility criteria
2. adherence to the BNDR and completion of ongoing, specified data collection
3. potential for self administration by the child or young person, or their parents/carers if they decide to administer treatments to their child, after appropriate training. You should take into account the family's level of social support and their home circumstances when deciding whether home administration is an option
4. involvement in decision making: the child, young person, and parents/carers should be actively involved in decision making about their treatment. You can help achieve this by making sure:
  - information is given to them in a format and at a level which they can understand
  - information includes the risks and benefits of the treatments being offered
  - the child/young person and family/carers are given time with a paediatric rheumatology clinical nurse specialist after their initial consultation with medical staff, to allow an opportunity to review the information, and facilitate informed decision making. This is likely to require more than one consultation
  - children/young people together with their parents/carers should be provided with support, education and training plans for home administration.
5. alternative protocols: children and young people may be given a biologic drug off license, after

consultation with their paediatric rheumatologist, based upon another indication. This should be clearly documented and supporting evidence written in the patient's medical notes. (Royal College of Paediatrics and Child Health's *Medicines for Children* gives helpful information on the use of off licence drugs – RCPCH, 2000)

6. drug availability: contact the prescribing hospital pharmacy to ensure that the drug will be available at the appropriate dosage for the child/young person
7. managing expectations: the parent or carer, and where appropriate the child/young person should recognise that there are criteria by which the benefit of treatment with etanercept or adalimumab will be assessed. They should be advised that if the treatment does not bring them significant clinical improvement, it is likely that the treatment with etanercept or adalimumab will be stopped.

## 2. Detailed assessment of patients

Full assessment of the child/young person, and accurate data collection about them, is essential both before treatment begins and throughout its course. The BSPAR guidance is set out in Appendix 9.

The assessment should include the following points:

1. haematology, biochemistry (including U&E), erythrocyte sedimentation rate (ESR) and anti-nuclear antigen, dsDNA in accordance with BSPAR, BNDR requirements. These tests should also fulfil the criteria for monitoring of other disease-modifying drugs co-prescribed with etanercept and adalimumab
2. height and weight prior to commencement of treatment, with drug doses calculated according to body weight
3. TB (attempting to screen patients in whom a Mantoux test is likely to be difficult to interpret due to previous immunosuppressive therapies requires a pragmatic approach)
  - assessment of risk factors + / – chest x-ray
  - baseline gamma interferon release assay for example T-SPOT TMTB test for TB
  - children and young people who have had TB should be excluded from biologic therapies
  - attention must be given to the presentation of TB in children and young people whilst biologic therapies are being administered. If the patient

has any of these high risk factors listed below, their case should be reviewed by the prescribing physician. You may also need to involve, depending on local policy, the paediatric respiratory consultant or infectious disease consultant for further assessment and investigation.

*High risk factors for TB are:*

- a personal or close family history of TB
  - lived in, or visited, a community with a high prevalence of TB.
4. live vaccines: **live vaccines must not be given during treatment and for six months following the completion of treatment.** This includes MMR, and BCG for TB, which should not be administered concurrently in patients receiving biologic therapies (see RCPCH (2002) *Immunisation of the immunocompromised child best practice statement* at [www.rcpch.ac.uk](http://www.rcpch.ac.uk). Also see *eligibility criteria Appendix 9*).

You should reinforce information about live vaccines to parents and carers verbally and in written format. Liaison with health visitors and school nurses is essential to ensure that any live vaccines are omitted whilst the child/young person is being administered biologic therapies. Problems can arise as immunisations in school are usually administered without the parent/carer being present. Parents/carers may have given consent to the full immunisation schedule months before the administration date, and may not be aware of the need to inform school that they need to withdraw their consent due to their child's treatment with biologic therapies, long-term steroids or MTX

5. consent: ensure the child/young person, as appropriate, and their parents/carers are accurately informed and prepared to continue with treatment. They must have signed the relevant consent form (if necessary for local policy). If no consent form is used in your trust, ensure accurate documentation of the information given to the child/young person and their parents/carers. Record that the consent of parents/carers (or if appropriate, the child/young person) has been obtained in the patient's medical notes
6. BSPAR criteria and BNDR: complete these, or liaise with the prescribing physician to support completion of the relevant data

7. psychological preparation: children and young people must be prepared psychologically for the treatment, in an age-appropriate manner. They will need information about: how, where and by whom subcutaneous injection will be delivered. It is essential, and if age appropriate, that the child/young person is involved in this decision process. Parents and carers also need adequate preparation, to ensure they can meet the needs of the child/young person
8. training for subcutaneous administration of biologic therapies at home: a training package is required to ensure the child/young person and their patient/carer understands their responsibilities in ensuring a supply and in concordance with treatment. The family also needs to understand about the safe handling, storage and disposal of etanercept or adalimumab and the associated equipment at home.

### 3. Before subcutaneous biologic therapies are administered

1. A paediatric rheumatology clinical nurse specialist or registered children's nurse with designated responsibility must be available to support and guide nurses or practitioners providing care for paediatric rheumatology patients.
2. The preparation of the injection must be undertaken according to the SPC of the drug, and administered within the stipulated timeframe that the drug is stable once reconstituted.
3. The paediatric consultant or their registrar must have assessed the child/young person is fit enough to commence treatment.
4. Checks before the first administration and ongoing assessments should include the following:
  - routine questioning about potential infectious contacts, for example TB or chicken pox. If an infection is suspected, consult the prescribing physician
  - confirmation from the parent/carer and if appropriate the child/young person that they are not aware of any inter-current infections
  - young women of childbearing age should confirm that they are using an effective method of contraception if sexually active. The age at which this information is discussed will be dependent on the maturity of the child/young person. If the young person is sexually active, it is

important that they realise biologic therapies taken by either males or females can potentially affect the development of a baby. Both males and females should be advised to use effective contraception whilst taking biologic therapies, and for six months after they have stopped taking the therapy. Reassure the patient that you and your paediatric rheumatology colleagues will advise them in complete confidence.

Further information about sexual health and young people is available at [www.brook.org.uk](http://www.brook.org.uk) which gives information about accessible sexual health clinics in their area (up to 25 year olds); [www.fpa.org.uk](http://www.fpa.org.uk) gives useful information for parents

- any allergies should be noted. It is essential that all allergies be taken seriously.

If you have concerns about abnormalities/infections, or doubts about whether treatment should continue, seek specialist advice from the paediatric rheumatology nurse specialist or prescribing physician.

### 4. Drug dosages

#### Etanercept

Etanercept for children and young people is prescribed at a dose of 0.4 mg/kg dose twice weekly. The total dose should not exceed a maximum of 25mgs twice weekly.

To avoid wastage paediatric packs of etanercept are available. The etanercept powder is reconstituted with bacteriostatic water which enables the vial once mixed to be stored for up to 14 days and for up to two doses used from each vial.

#### Adalimumab

Adalimumab for young people aged 13-17 years is licensed as a fixed dose of 40 mgs which is administered on alternate weeks.

Two formulations are available either a pre-filled syringe or a pen.

### 5. Follow-up care between treatments

Even if families become self sufficient in the administration of etanercept or adalimumab at home, they must continue to be monitored as problems with compliance are not uncommon, particularly with adolescent patients.

After their treatment, ensure that the child/young person and their family are given:

1. **contact details:** ensure that the family are given these, both verbally and written, for normal and out of hours queries. Out of hours contacts will be dependent upon local services and the on-call arrangements within your paediatric rheumatology team
2. **next treatment date:** the date, and where they need to have drug monitoring/bloods taken
3. **date for full assessment and review of treatment:**
  - a. *etanercept:* this should initially be three monthly, and then continue three monthly if the child/young person's condition allows, and for one year after treatment has stopped. BNDR data is collected at baseline, three months and annually
  - b. *adalimumab:* should also be a minimum of three monthly.
4. an understanding of the importance of *the need to attend* for regular medical/AHP reviews
5. **Biologic Therapy Alert Card:** give these to young people to carry with them to inform others that they are on biologic therapies. (These are available from [www.arc.org.uk](http://www.arc.org.uk)).

## Section 2: Resource planning for children and young people

As a specialist paediatric rheumatology practitioner, it is your responsibility to ensure that appropriate resources are available to provide safe and effective treatment for children/young people in your unit. Each unit will have particular strengths and weaknesses in their team skill mix, level of medical support and facilities.

Appendix 7 on resource planning sets out the key issues for resource planning for service redesign. Here, in *Part 2: Children and young people*, we have highlighted particular issues for the care of children and young people which you will need to take into account when planning services which involve paediatric and adolescent care and treatment. This is purely an advisory document and you will need to develop guidance that is tailored to meet local needs.

You will find a key list of documents to access before planning service provision of biologic therapies in reference sections. *Note that when using adult sections on resource planning, you will need to substitute 'specialist rheumatology practitioner' with 'paediatric rheumatology clinical nurse specialist'.*

### 1. Biologics Register

Whatever the structure of your local paediatric rheumatology service, it is very important that you recognise the importance of collecting data for the BSPAR, BNDR.

When reviewing and planning your local service needs you will need to allow for extra time to collect data for the BNDR.

### 2. Providing a seamless service

Due to the distances some children and young people often need to travel to access specialist paediatric rheumatology services, shared care arrangements are often instigated. These arrangements must be highly organised and robust to maintain a safe, efficient

service. Everyone involved in delivering care must be fully informed and competent in the specialist care required by children and young people and their parents or carers.

Close liaison is also required between the specialist hospital services, primary health care teams and educational teams, especially when these professionals are directly involved in the administration and support of children and young people receiving biologic therapies.

### 3. Tailoring support from pharmaceutical companies

Some rheumatology units work with pharmaceutical companies which provide nurses to support care of children and young people. It is important that all nursing staff involved in this care are specifically assessed for their competency to work with children and young people. This includes assessment of:

- ◆ child protection issues
- ◆ paediatric clinical skills
- ◆ attitudes to children and young people
- ◆ communication skills with children, young people and parents/carers.

Not all staff employed by pharmaceutical or drug distribution companies will be able to meet these criteria. For more information, see the NMC/UKCC 1997 guidance, *Working in posts not related to your registration status*.

If pharmaceutical companies support new posts, you will need to ensure that the employing NHS trust is committed to ensuring that the new position will be substantive once pharmaceutical funding ceases, especially if the post is directly attributable to the administration and ongoing monitoring of treatments.

### 4. Specialist expertise and skill mix

The RCN Working Party identified three levels of competency to help paediatric rheumatology clinical nurse specialists recognise the range of skill mixes that may be used in planning the provision of care.

Whatever the skill mix, it is essential that it includes adequate paediatric rheumatology clinical nurse specialist support for children and young people receiving biologic therapies.

# Appendix 1

## Patient Management Workbook

An aid to standardised assessment and management processes for delivering biologic therapies.

The workbook can be modified for local use; to access an on-screen, Microsoft Word version, see the Rheumatology Professional Communities section of the RCN website, at: [www.rcn.org.uk/rheumatology](http://www.rcn.org.uk/rheumatology).

### Patient label:

<b>Section 1: Disease specific eligibility criteria</b>	
<b>Ankylosing spondylitis</b>	
<b>AS (12 weeks apart)</b>	
BASDAI 1	
Sp VAS 1	
BASDAI 2	
Sp VAS 2	
<b>Psoriatic arthritis</b>	
<b>PsA: 1 month apart</b>	
<b>Using 76 swollen 78 tender</b>	
1st: Tender joint count	
1st: Swollen joint count	
2nd: Tender joint count	
2nd: Swollen joint count	
1st: Patient global	
2nd: Physician global	
<b>Rheumatoid arthritis</b>	
<b>Disease Activity: 1 month apart</b>	
<b>Using DAS 28 assessment</b>	
<b>RA</b>	
Tender joints	Swollen joints
ESR/CRP	Global health VAS
DAS 1	DAS 2

<p><b>Section 2: Exclusion criteria</b></p> <p><i>Tick when checked and refer to prescribing physician if any exclusion criteria identified.</i></p> <p>Refer to drug SPC for additional information</p>	Tick box
Known sensitivity to therapy or component parts (e.g. murine products)	
Pregnant or breastfeeding (effective contraception must be used)	
Suspicion of malignancy – requires further investigation seek medical opinion	
Active infection or patients at high risk of infection. Examples include:	
<ul style="list-style-type: none"> <li>• chronic leg ulcers</li> </ul>	
<ul style="list-style-type: none"> <li>• previous tuberculosis or risk factors (see section below TB assessment)</li> </ul>	
<ul style="list-style-type: none"> <li>• septic arthritis of a native joint within the last 12 months or sepsis</li> </ul>	
<ul style="list-style-type: none"> <li>• prosthetic joint within the last 12 months. Excluded indefinitely if the joint remains in situ</li> </ul>	
<ul style="list-style-type: none"> <li>• persistent or recurrent chest infections</li> </ul>	
<ul style="list-style-type: none"> <li>• other infections</li> </ul>	
<ul style="list-style-type: none"> <li>• moderate or severe congestive heart failure (New York Heart Classification (NYH) III or IV).</li> </ul>	
<p>Patient eligible for treatment?    Yes    No</p> <p>If no, state reason for exclusion:</p>	

<p><b>Caution – review with prescribing physician</b></p>	Tick box
<ul style="list-style-type: none"> <li>• Acute or chronic hepatitis B or C, or HIV</li> </ul>	
<ul style="list-style-type: none"> <li>• Index of suspicion for TB risk</li> </ul>	
<ul style="list-style-type: none"> <li>• Chronic respiratory conditions including: interstitial lung disease, chronic obstructive pulmonary disease (COPD) or abnormal chest x-ray</li> <li>• If evidence of COPD in patient to be considered for abatacept therapy</li> <li>• History of pneumocystis jiroveci pneumonia (PCP) and prescribed high dose steroids</li> </ul>	
<ul style="list-style-type: none"> <li>• Evidence of any pre-malignant conditions including: <ul style="list-style-type: none"> <li>- Barrett’s oesophagus</li> <li>- cervical dysplasia</li> <li>- large bowel polyps</li> <li>- non-melanoma skin cancer</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>• Signs of chronic congestive heart failure (CCF)</li> </ul>	

<b>Section 3: Screening prior to treatment</b>				Tick box
<b>Tuberculosis assessment of immunity/risk</b>				
BCG scar	Yes	No		
Mantoux required	Yes	No		
Quantiferon or TB spot test	Yes	No		
Result	Date			
Chest x-ray	Date			
Report				
Information sheet given?	Signature	Date		
<i>NB: chest x-ray should taken as close as possible to the time before starting treatment</i>				
<b>Tuberculosis risk factors/additional respiratory factors to consider</b>				
Note: specific respiratory symptoms, e.g. cough productive of blood stained sputum, or any signs of respiratory infection: TB travel risk factors for individual or close relatives (e.g. frequent travel and residency in areas of high prevalence for TB) If increased risk factors identified discuss with clinician re additional screening				
Referred to TB clinic	Yes	No		
Result:				
Check result of TB testing before proceeding				
<b>(See BSR/BTS guidelines if previously treated TB)</b>				
Note: for respiratory disease and history, may be helpful to calculate smoking history according to pack years. For example: Number of cigarettes per day (40 cigarettes) divided by 20 and multiply by number of years (10 years) a person has smoked. $40 \div 20 = 2$ . $2 \times 10$ years = 20 pack year history				
<b>Immunisation</b>				
Pneumovax immunisation	Yes	No		
Varicella Zoster status:	Yes	No		
Exposure to recent infections (shingles/chicken pox)	Yes	No		
Hepatitis B assessment required	Yes	No		
Hepatitis C assessment required	Yes	No		
Risk factors for hepatitis B/C include:				
<b>Other:</b>				
Skin Check (PsA)				
Throat:				
BP	Pulse	Weight	Height	Urinalysis
Blood tests checked:				
Abnormalities noted:				
Note any attendance for regular health checks and results if appropriate. For example, cervical screening for women.				
Note any investigations pending with other specialist areas: e.g. dermatology for skin investigations				
<b>Further Investigations required: Specify</b>				
<b>Review date:</b>				
Drug to be prescribed:	Dosage	Frequency		
Combination therapy:	Drug	Dosage	Frequency	

**Section 4: General and infection screening***If malignancy or infections identified, specify these.***Malignancy:**

Type:

Date of diagnosis:

**Review following initial screening for treatment criteria****Infections:** Type:

Date of last infective episode:

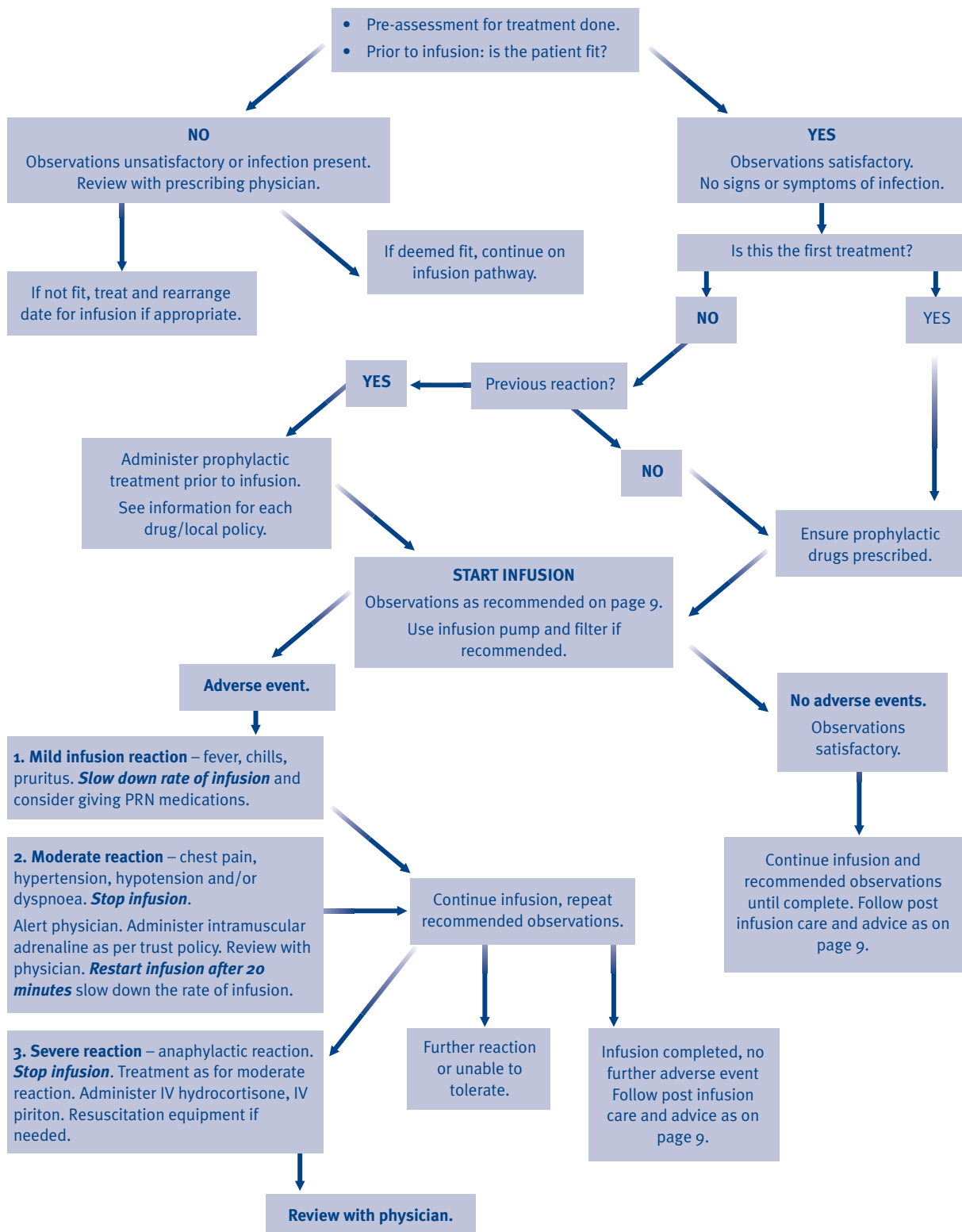
Treatment:

<b>Consent guidance</b>	<b>Yes</b>
Has the patient been fully informed about treatment?	
Has the patient had an opportunity to ask questions?	
Has the patient been provided with written information?	
Has the patient given informed consent to treatment and information being shared with the BSR Biologics Register if required?	
Has consent been documented in the patient's notes?	
Local trust consent policy completed if required?	
Are all the pre-treatment screening tests completed?	
If appropriate, has the patient been prescribed MTX?	
If required, has the BSR Biologics Register data been collected?	

# Appendix 2

## Flow algorithm for patients receiving intravenous biologic therapy

Use in conjunction with guidance section, page 9



## Appendix 3

# The British Society of Rheumatology Biologics Register (BSRBR)

The BSRBR is the largest prospective register of rheumatology patients receiving anti-TNF $\alpha$  therapy in the world, and at the time of publication had registered over 15,500 patients. The BSRBR is a valuable and ongoing observational research study for adults treated with biologic therapies. The data collected from this registry has provided vital early evidence of the clinical experience of treating people with biologic therapies against a control group receiving traditional DMARD drugs.

Although randomised controlled trials have demonstrated the efficacy of many biologic therapies, BSRBR observational data will provide invaluable evidence over the long term (10 years) based upon experience in routine clinical practice. Importantly, the register has been designed to monitor the long-term safety profile of these agents. The register is a unique collaboration between the University of Manchester, the BSR (a medical professionals' society) and the pharmaceutical industry. All consultant rheumatologists in the UK who prescribed anti-TNF $\alpha$  therapy participate in the register, supported by nurses and other health practitioners. Health care professionals and patients are required to complete questionnaires on a regular basis. Professionals complete clinical questionnaires to report changes in health status or new investigations, while patients are requested to complete a number of patient-reported outcomes and a patient diary.

The BSRBR tracks the progress of patients with severe RA and other rheumatic conditions being treated with anti-TNF $\alpha$  therapies (adalimumab, etanercept and infliximab) and rituximab for RA and AS. The register no longer requires new patients to be registered who have RA, AS or PsA and are being treated with adalimumab, etanercept or infliximab. However, the rituximab registry is recruiting for RA.

Registration criteria and assessments required will vary depending on the condition, recruitment timeframes and new therapies being included on the register. For the most up to date information on data collection requirements, and for access to tools to assess patients for the register refer to:

[www.medicine.manchester.ac.uk/epidemiology](http://www.medicine.manchester.ac.uk/epidemiology)).

## Appendix 4

# Training patients to self administer subcutaneous biologic therapies: a framework for registered rheumatology nurses

*Modified from guidelines developed for the treatment and monitoring of MTX therapy by the University Hospital Birmingham NHS Foundation Trust, with kind permission.*

*You will find additional resources, such as guidance on self-administration of subcutaneous MTX and supporting protocols/guidelines, at the RCN Rheumatology Forum website: [www.rcn.org.uk/rheumatology](http://www.rcn.org.uk/rheumatology).*

*Refer to Part 1, Section 1, Screening, page 5 for guidance on issues of consent.*

### Review of clinical practice and skills

A lead nurse in the rheumatology team should maintain a list of registered rheumatology nurses who are competent in training patients to self administer. The lead nurse must ensure that relevant audits are undertaken to check adherence to the protocol with support of the clinical governance department. The audit will be undertaken in accordance with the review date documented on local policies or guidelines.

### Clinical incident reporting and management

Any untoward incidents and near misses should be reported using an incident report, and dealt with by the appropriate management team. The risk management team must be notified by telephone of any serious untoward incidents.

### Planning care

The aim for the nurses trained to educate patients is to enable the patient to become competent in self administering a subcutaneous injection, so that they can become independent and able to inject themselves at home. In some cases patients may nominate a partner, carer or parent to administer the injections for

them. Once the patient or carer is competent and stable, you can arrange delivery of the equipment and drug therapy to the patient's home through the home care service or directly from the rheumatology department.

Patients and carers will need training to ensure safe storage, handling and administration of biologic therapies (Dougherty *et al.*, 2005). Guidance must include handling and storage of the drugs, as well as injection technique principles such as rigorous hygiene and safety procedures in using medications and the equipment used for injection.

Patients/carers should receive verbal and written information specifically developed to support the training programme, as well as medication information sheets such as those produced by arc. A biologic alert card should be provided to every patient. These can be obtained from the arc website ([www.arc.org.uk](http://www.arc.org.uk)) but are usually also provided in the patient information packs produced by the pharmaceutical companies manufacturing the therapy.

Following the training programme, you should also provide appropriate follow up and telephone support (NMC, 2007). Patients must be advised that they will require regular monitoring and review to ensure they are achieving treatment benefit. Blood monitoring is carried out in accordance with the hospital's monitoring protocols.

### Flexibility in level of training

Practitioners need to be flexible in their training methods according to the patient and carers' learning needs, and after discussion and assessment of their competence in administration techniques. You should agree a training package with the patient/carers. Some patients/carers will require a greater number of practice sessions, and you will need to tailor the level of supervision you give before the patient is confident and competent.

In many cases patients with inflammatory joint disease will already be competent in subcutaneous injections as they will have been self administering MTX (a cytotoxic therapy) or for other co-morbidities such as osteoporosis. In a very small number of adult cases, patients are unable to self administer their treatment. In these circumstances, and if the patient consents, a carer can be taught to administer the injection.

### Home care services

Home care services are available for many patients receiving subcutaneous biologic therapies, provided by the pharmaceutical companies which produce the drugs. This community support can include provision of nurses competent to train patients at home, as well as delivery of the drugs and collection of sharps boxes and clinical waste. Home care services such as these do not incur any additional charges for VAT on the cost of the drugs. It will be at the discretion of the rheumatology department with reference to local trust policy and with the support of the pharmacy department, to decide on the package of care most appropriate for the individual patient.

Note that training videos/DVDs are available from the pharmaceutical companies to support your training programme.

In many cases, however, and depending upon local provision, patients may elect to be trained to self administer their subcutaneous biologic therapy supported by their usual team from the rheumatology department.

### For subcutaneous treatment to go ahead

1. A specialist with appropriate prescribing qualifications who can prescribe an anti-TNF $\alpha$  therapy must be available. Other biologic therapies may need to be prescribed by a medical specialist in the field. Refer to the SPC and where appropriate any regulatory guidance documents (such as NICE).
2. A registered rheumatology nurse should assess the patient's/carer's understanding of the process by discussing the training programme with them (see more detail below).
3. The patient must fulfil the treatment criteria.
4. To receive a programme of tuition for self/carer injection of subcutaneous therapies at home, you must have assessed the patient/carer to ensure they:
  - ◆ are aware of the reason for treatment

- ◆ have the ability and the willingness to administer injections
- ◆ understand storage, equipment and handling conditions (see patient training package, page 49, for detail)
- ◆ understand what to do when experiencing side effects
- ◆ understand the importance of attendance for monitoring.

### Contraindications for patient self administration

1. The patient declines treatment/the training programme.
2. Patients and carers:
  - ◆ are unable to administer the injection because of poor dexterity as indicated in a practical demonstration to the rheumatology nurse, and if they do not elect to have a carer to administer treatment instead
  - ◆ show poor concordance with attendance and monitoring
  - ◆ are unable to safely store the injections at home or are unable to demonstrate an understanding of the need for safe storage
  - ◆ demonstrate a lack of understanding of the safety and self care requirements.
3. If, in your professional opinion as a registered rheumatology nurse, you consider the patient's condition requires that the injection should not be administered (for example, skin rashes, infection, neutropenia, leucopenia, thrombocytopenia, abnormal liver function tests, pregnancy, breast-feeding and planning to conceive). In these cases, seek a medical opinion.

*The patient must be referred for a medical opinion if they:*

1. develop a new health problem or an existing health problem requires medical supervision
2. have poorly controlled side effects or develop toxicity to their treatment
3. have evidence of developing a blood dyscrasia
4. have failed to respond to treatment and there is evidence of disease progression.

### Continuing management

On completion of the training programme and when the patient/carer has demonstrated competence in all aspects of administration, you should inform them of the follow-up arrangements. If a home care company is taking over delivering the treatment, the home care service should be notified and informed of the patient's progress. The patient must be provided with the necessary equipment by the department or the home care company.

## Patient training package to self administer subcutaneous biologic therapies

### Introduction

Self management is a pivotal aspect of health policy for individuals with long term conditions, encouraging patients to actively manage their own treatment regimes including administering their own subcutaneous injections in a similar way to patients injecting insulin. Self-administration of therapies also can improve patient choice and reduce the need to attend hospital appointments and reduce reliance on the health care system. In addition, it allows the patient to pursue their normal activities of daily living without the disruption of attending a health centre or clinic to receive treatment. The framework outlined is a guide to enable practitioners to instigate a programme of patient self-administration of subcutaneous biologic therapies.

This patient training package is published as part of, and should be used with, the Royal College of Nursing (2009) *Assessing, managing and monitoring biologic therapies for inflammatory arthritis: Guidance for rheumatology practitioners*, which looks in detail at the total care of patients receiving biologic therapies. It may also be helpful to refer to *Administering subcutaneous methotrexate for inflammatory arthritis* published by the RCN (2004).

The expertise of the specialist practitioner is to recognise and provide support in administering the most appropriate treatment for each individual patient. Patient preference for a specific treatment option will vary depending on a number of factors, including:

- ◆ the patient's medical history and functional ability
- ◆ social factors
- ◆ psychological aspects of treatment options.

For more detailed information on all subcutaneous biologic therapies refer to their SPC and to the research evidence set out in the reference section of the main RCN guidance.

### Criteria for patient selection

To select patients and carers for self-administration of subcutaneous injections, you must ensure that the patient:

- ◆ fulfils the criteria for treatment of biologic therapies\*
- ◆ consents to taking part in the educational programme
- ◆ gives their consent to treatment and to self-administration of the drug (or administration by nominated carer).

and that the patient or nominated carer:

- ◆ is willing to administer injections
- ◆ has the ability to administer injections
- ◆ has the ability to store syringes/drugs safely (including keeping equipment and drugs locked away from children) and transport injections
- ◆ understands the conditions of handling all the equipment and how to deal with spillage, disposal of sharps and waste while at home
- ◆ can be provided with an effective and safe method of collection and disposal of the drug and equipment
- ◆ understands the factors to consider, and action to take, when experiencing side effects
- ◆ understands the importance of attendance for follow-up and monitoring.

### Reasons for exclusion

- ◆ You, as a registered practitioner, believe the patient's condition necessitates withholding treatment. In this circumstance, you should refer the patient to the prescribing consultant rheumatologist.
- ◆ The patient is unable to adhere to any of the eligibility criteria.

If the patient fails in any of the treatment criteria, you should liaise with the prescribing consultant and patient to plan their treatment options.

\* For more details of general screening and eligibility criteria see Part 1, Section 1 of the main RCN guidance.

## Procedure

- ◆ A prescribing specialist formally requests and prescribes the initial treatment, stating dose and route of administration.
- ◆ The patient meets the eligibility criteria to be trained in self administration set out above, and completes the training programme.
- ◆ Once the patient has successfully completed the programme, a letter is sent to the patient's general practitioner.
- ◆ The patient is given access to a telephone advice line service and emergency contact number.
- ◆ If the patient/carer fails to meet the requirements for self-administration, the specialist practitioner will liaise with the prescribing rheumatologist to plan an alternative for the patient's care.

## The training programme documentation

*The documentation provided to nurses delivering training should include:*

Planning, training for, and delivering care (see below)

References

*Plus:*

Education package for patients and carers

Form: Requirements for home administration of subcutaneous biologic therapies

Patient agreement form for home administration of subcutaneous biologic therapies

Check list: Requirements for home administration of subcutaneous biologic therapies

Patient consent form

Evidence of supervised practice by patient

## Planning, training for and delivering care

### Outline of care

The consultant rheumatologist or specialist practitioner will undertake a medical examination of the patient prior to treatment and will ensure that they meet the eligibility criteria for treatment according to the BSR and relevant NICE criteria for treatment with biologic therapies. In cases where the patient fails treatment criteria but there are specific circumstances deemed

necessary by the prescribing physician a specific request for funding will need to be sanctioned by the commissioner/funder who will determine whether to fund the treatment. Such procedures need to be clearly documented in the notes.

Eligible patients who wish to proceed with the treatment may then commence the educational programme. The specialist team should write formally to the patient's general practitioner requesting support for the monitoring of treatment, subject to the patient completing a successful educational programme. Depending upon local service provision, the specialist team may be responsible for ongoing management or this may be shared with General Practitioners with a Special Interest or an advanced specialist nurse practitioner. Current service innovations may result in different management approaches in providing ongoing support. The nurse/practitioner should advise the patient on follow-up care and ensure that the patient is aware of the treatment plan, including details of the first point of contact in case of any queries or problems.

### Support for patients at home

These specific home care packages will require co-ordination with the specialist nurse team instigating biologic treatments. See *Home care services* on page 48.

### Planning care

Your aim is to ensure the patient can become competent in the self-administration of subcutaneous injections, in their own home. Once the patient (or carer) is competent and stable, either you or the health care organisation providing training within the community setting, can arrange delivery of treatment and equipment to their home. If you wish to instigate the patient's training programme within your specialist unit, you must ensure adequate continuity of care by ensuring adequate provision for delivery of the drug therapy and equipment. This may mean transferring ongoing deliveries to a health care organisation charged to provide this service within the community.

The role of nurses in continuity of care include:

- ◆ providing education
- ◆ obtaining informed consent as and when required for treatments or change in treatments
- ◆ assessing, administering and providing regular follow-up care (including blood monitoring) and screening for any adverse effects of treatment
- ◆ data collection and completion of information for the Biologics Register where required

- ◆ telephone advice line support and ongoing monitoring and disease assessment (RCN, 2006).

### Training the patient or carer

Training of patients should be supported by an educational training package for the patient, and where appropriate allow the patient to review the different administration packs so they can compare for preference in injecting.

The number of practice sessions which need supervision will vary for individual patients. You should take into account the patient and carer's learning needs after discussion and assessment of their competence in technique. This will be based upon a mutually agreed educational package provided to the patient. The number of training sessions to achieve competency will be determined by you and the patient and will vary from patient to patient and choice of drug delivery system.

### Ongoing management

Upon completion of a satisfactory training programme, you should liaise with the home care organisation to ensure they are adequately informed of the patient's progress.

The patient must have the following equipment:

- ◆ a cool bag for collection of auto-injector, vial or pre-filled syringes (for patients collecting their medication)
- ◆ sharps disposal bin
- ◆ medswabs
- ◆ cotton wool balls
- ◆ plasters.

The patient should be provided with:

- ◆ the date and time of their next blood test and outpatient appointment
- ◆ advice on telephone contact (telephone advice line and/or general practitioner services). For standards of telephone support refer to the *RCN guidance on the use of telephone advice line services for long term conditions* (2006).

The pharmaceutical industry constantly strive to improve the administration of the biologic therapy by introducing modifications or new delivery devices, such as introducing pre-filled syringes or auto-injectors. Patients who are stable on a biologic drug who are changing from one injection device to another should

be offered additional support and training (Hiley *et al.*, 2008).

Patients who travel may also request a letter (from the specialist team or independent organisation who provide medications to them at home) to confirm the need to carry needles and syringes with them whilst travelling abroad. It is useful to develop a template that can be used for such circumstances.

### Suggested training materials for self administration of biologic therapies are set out on page 52.

For additional information/guidance and pictures to show your patients, refer to RCN *Subcutaneous methotrexate guidelines*, (2004).

## Information for patients and carers: administering your own injections of biologic therapies at home

### Rheumatology department:

#### Patient's name:

Make sure that these instructions are always nearby in case you have any queries or problems.

Remember that you can telephone the rheumatology specialist nurse on their advice line number.

#### Advice line telephone number:

An answerphone service will record calls whilst the nurses are in clinic. A nurse will return your call as soon as possible.

If the problem is more urgent, or it is out of normal working hours, please telephone your own doctor. If the health centre is closed there will be advice to tell you how to access help out of hours.

#### Your doctor's number:

### Equipment

There are a number of different methods that can be used to help you give yourself an injection. The package containing your treatment will come with either:

- ◆ syringes or needles for your injection, together with small glass vials containing the medication you have been prescribed
- ◆ a pre-filled syringe or pre-filled pen that contains your medication, or
- ◆ an auto-injector.

You must store this medication in the fridge, whatever type of equipment it comes in. Along with your medication, you will be sent detailed information about how to store it. Please read this information carefully. If you have queries, contact your specialist nurse/practitioner or the company responsible for delivering your injections to you at home.

The package usually contains:

- ◆ alcohol wipes
- ◆ cotton wool swabs (small pads of cotton wool)
- ◆ plasters
- ◆ a sharps box for disposing of used needles and syringes
- ◆ information leaflet.

### Information leaflets

The company providing your treatment has prepared a patient information leaflet about how to inject yourself using the treatment prescribed for you. This information is included in the package containing your injection and equipment. Please read the details carefully. Your rheumatology department may also provide extra information about your treatment.

### Supplies of treatment and equipment

Make sure you know when and how your treatment will be delivered to you at home. You also need to know how the sharps box and other clinical waste will be disposed of. Do not put the sharps box into the dustbin – used needles and syringes are a hazard. The sharps box must be disposed of safely and should be collected by your home care team or delivered to the hospital or community hospital.

### How to give biologic therapies by subcutaneous injection

(Subcutaneous means under the skin)

#### Getting ready

1. Don't rush – make sure you have plenty of time. As you get used to giving the injection, you will find it much easier. Make sure that there are no distractions, such as children or animals in the room.
2. Wash your hands and dry them.
3. Take your injection pack or auto injector/pen from the fridge. Put it on a clean, flat surface. You should leave the auto-injector flash pen to reach room temperature before injecting, this helps reduce the risk of reactions.
4. If using vials of freeze-dried drugs, prepare them according to the special information provided to you in the drug packaging.
5. Take out the injection from its protective packaging. The package should include (or you should have available) an alcohol wipe, a cotton wool swab and a plaster. Put them in a small polythene container. Have sharps box close at hand.
6. Decide where you will put the injection – either under the skin of your tummy or in the front of your

thigh. This is your injection site. Choose a different side of your tummy or opposite thighs each time you inject.

7. Read and check the label, dosage and expiry date on the bottle. If the expiry date has passed, do not inject the drug but contact your pharmacist or specialist nurse/practitioner to arrange replacement supplies.
8. Clean the area of skin you are going to inject with an alcohol wipe (mediswab). Allow a few seconds for the skin to dry.

### Giving the injection

1. Do not shake the syringe/auto injector or pen.
2. If the liquid in the syringe has particles or is not clear, do not inject the fluid. Contact the pharmacy or specialist nurse/practitioner about it.

### Giving the injection using a syringe and needle

1. Remove the sheath from the needle. Make sure that you do not touch any part of the needle while you are preparing the injection.
2. Pinch the skin around the area you have wiped clean. Insert the needle into the skin at 90 degrees (pointing directly down onto the skin, at right angle (90 degrees)). The needle is only half an inch (about 1.5cm) long, and will deliver the injection just below the skin. Push the plunger gently all the way down, then hold the syringe in that position for a couple of seconds until you see all the fluid has left the syringe.

### Giving the injection using an auto-injector pen

1. Remove the cap(s) from the pen as instructed in your packaging.
2. Pinch the skin around the area you have wiped clean. Place the injection end of the auto injector pen against the skin, at right angle (90 degrees) pointing the injecting end straight down onto the skin. Make sure you can see the small window on the auto injector – it should be facing you. You need to have the window facing you so you can see it change colour when you have successfully given the medication.
3. Push down on the plunger, or section of the device as you have been instructed, to activate the injection. Hold in position for a few seconds.

### After you've given the injection

1. Withdraw the needle and syringe/auto-injector/pen and cover the injection site with a cotton wool swab.
2. After a few seconds remove the swab, and cover the injection site with a plaster.
3. Do not put the cover back on the needle or tamper with the auto injector pen, or you may prick yourself. Just discard the syringe and needle into the sharps box, along with the alcohol wipe and cotton wool swab.
4. You may notice bleeding or bruising at the injection site. Don't worry, this happens when a small blood vessel is punctured by a needle. If there's bleeding, apply a cotton wool swab and maintain gentle pressure for a minute or two until bleeding stops. The bleeding will soon stop and any bruising will disappear.
5. Make a note of when your next injection will be due – and ensure that you have enough of the treatment available.

**IMPORTANT NOTE:** Do not put any of the equipment you have used in your normal household rubbish. Use the sharps box provided.

### After care

**If you experience a rash or discomfort around the injection area:** Sometimes when people receive a subcutaneous injection, some of the injected fluid may leak into the surrounding skin and cause irritation around the injection area. This will normally settle in a few days. If you have a severe rash or you are concerned, seek advice from your specialist team.

If you notice irritation or redness in the injection area that does not settle after three days, you should contact your GP. They might prescribe a hydrocortisone cream to stop the irritation.

**If your carer accidentally pricks themselves with the needle:** If your carer gets a needle-stick injury after they have given you the injection, they must make the injury area bleed as much as possible while running it under a cold tap for at least 10 minutes. It is advisable for them to seek guidance from your GP's surgery or telephone advice line. You and your carer may need to answer a few questions to help the doctor or nurse decide if any treatment is needed.

## Patient agreement form for home administration of subcutaneous biologic therapies

Name:

Date:

You have been taught how to give your injections by the subcutaneous route.

On ..... occasions you have given the injection under the supervision of the rheumatology nurses. They now consider that you are competent to give these injections at home, using the techniques you have been taught. Before this happens it is important to check that you are happy to do this and that you fully understand the procedure.

Please read the statements below and sign the appropriate box:

	Yes	Patient initials
1. I have been given written information on how to give injections		
2. I have been given information about my treatment		
3. I have a fridge at home where I can safely store the injections		
4. Young children have access to my fridge at home		
<b>If you have answered yes to question 4, please answer question 5</b>		
5. I understand that I must keep the injections in the fridge and out of reach of young children		
6. I can manage the syringe without difficulty		
7. I can show the areas where I can give injections		
8. I am confident that I can give the injection subcutaneously (under the skin)		
9. I know that I must safely dispose of the needle and syringe in the sharps box provided, and have been advised on how to manage spillages		
10. I know what to do if I have a problem		
11. I understand how my sharps box and other waste material will be disposed of		
12. I recognise my responsibilities in: <ul style="list-style-type: none"> <li>• reporting infections promptly, and</li> <li>• attending for monitoring and follow-up care.</li> </ul>		

## Appendix 5

# Detailed guidance for screening and managing TB

Evidence shows that there is an increased risk of infections and emergence of latent TB in patients receiving some biologic treatments, so it is essential that practitioners ensure patients are thoroughly screened. Many patients receiving biologic therapies have complex chronic disease and will have received immunosuppressant therapies in the form of disease-modifying drugs and steroids. They are also at risk from other comorbidity factors associated with their complex disease and poor general health.

Ongoing observational studies, post marketing surveillance and clinical trials (Dixon *et al.*, 2008) have identified that re-activation of latent TB needs to be carefully considered for patients treated with anti-TNF $\alpha$ , particularly as TNF $\alpha$  has a pivotal role in containing bacilli within granulomatous lesions. Patients receiving other non TNF $\alpha$  biologic therapies have already been subject to rigorous screening before treatment. The evidence therefore needs to consider the need for vigilance with all biologic therapies until further research evidence is available. To date, however, there have been no reports of TB in patients treated with rituximab or anakinra.

### Screening

If local trust or British Thoracic Society (BTS) Guidelines are available, you should follow these when screening patients. However, a brief outline is included here to guide you in the principles of routine screening for all patients before treatment with biologic therapies is commenced.

All patients should be assessed for risk of TB by taking a full patient history and reviewing the recent chest x-ray and physical examination.

#### 1. Detailed patient history:

- ◆ current respiratory symptoms
- ◆ personal or close family history of TB
- ◆ previous BCG vaccination, observe for evidence of a scar. White patients born before 1942 will not have been part of the routine BCG immunisation programme. Patients from ethnic minority groups should have been given BCG at birth if born in the UK, or have been tuberculin tested and BCG

vaccinated if negative, after arrival – but it is known that coverage of these immunisation programmes was not complete

- ◆ place of birth. Has the patient lived outside the UK for six months or more in an area with high prevalence of TB (40/100000pa: all countries, apart from the current EU, Australia, New Zealand, USA and Canada)?
- ◆ identify patients who currently live in an area with high prevalence of TB in the local community. For guidance on local prevalence seek advice from the local respiratory consultant.

**2. Chest x-ray:** patients should have had a chest x-ray as close as possible to the proposed treatment start date, and no longer than the last three months before treatment. If they are currently experiencing persistent respiratory symptoms, they need to be given a repeat chest x-ray. This should be reviewed by the prescribing physician.

**3. Physical examination:** this should include examination of the chest, noting any abnormal clinical signs. Report to the prescribing physician or member of the medical team.

**4. Tuberculin test (skin test):** in the UK, this is normally a Mantoux test. Skin testing should not be undertaken on:

- ◆ patients who have had previous treatment or chemoprophylaxis for TB, have evidence that TB is present or have x-ray evidence of TB scarring
- ◆ patients who have been recently prescribed immuno-suppressive therapy (< 2 months) such as steroids, azathioprine, MTX, ciclosporin etc.

Note: False negative skin tests are common. Immunosuppression due to drug therapy, active inflammatory disease or advancing years all weaken, or even abolish, the skin test response to tuberculin.

#### T spot and QuantiferonTB Test (blood test)

Evidence suggests that T spot test is more sensitive to picking up latent and active TB than the tuberculin skin test. This test may not be available in all units and is costly. In some circumstances, a cost-benefit analysis

based upon the risks within the local population or patient being screened may be helpful.

Quantiferon has not been specifically validated in the inflammatory arthritis patient group. The same principles of use apply to Quantiferon as to T spot, until further guidance is published. (Refer for further information to the BSR guidelines for the management of biologic therapies, BSR, 2009).

### High risk patients

Patients who have any of the high risk factors listed below should be identified for review by the prescribing physician. It may be appropriate to involve the local chest physician for further assessment and investigation:

- ◆ current respiratory symptoms,
- ◆ a personal or close family history of TB
- ◆ lived in a community with a high prevalence of TB
- ◆ an abnormal chest x-ray.

### Treatment for TB

#### Anti-TNF $\alpha$ therapies

Patients with symptoms or radiological signs suggestive of active TB must be investigated appropriately. If active TB (i.e. tuberculosis disease) is diagnosed, then treatment following the BTS Guidelines should be started. In general, treatment with anti-TNF $\alpha$  should be delayed until prophylactic treatment is complete. Seek guidance from a respiratory physician.

We suggest that treatment with biologic therapies for inflammatory disease should be delayed until the patient has received anti-TB treatment for two months

with monitored compliance. However, in cases where patients have severe disease, a risk benefit analysis by the prescribing physician should be undertaken.

If cultures for *M. tuberculosis* are available, antibiotic susceptibility data should be known to ensure the patient is receiving appropriate treatment. For patients who may have been previously infected with TB, but who do not have active TB at the time of assessment, there is a risk that treatment with biologic therapies will reactivate their tuberculosis infection. TB therapy (chemoprophylaxis) can reduce the risk of reactivation. However, the possibility of reactivation of TB has to be balanced against the risks of morbidity and mortality from the anti-TB drugs – risks which are increased in the elderly (Saag *et al.*, 2008).

Practitioners are advised to refer to the BTS website to check for future updated guidance ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)).

#### Rituximab

Although there is to no evidence to date of a risk of TB or latent TB reactivation with rituximab patients, it is important to note that patients currently receiving rituximab are usually eligible for treatment because they have failed anti-TNF $\alpha$  therapies and therefore will already have been subject to pre-TB screening. Vigilance in monitoring should be maintained for all biologic therapies even when specific pre-treatment screening is not required.

#### Information for patients

Patient information sheets on anti-TB therapy are available on the BTS website (available in English, Punjabi, Hindi, Gujarati, Somali, Turkish, Urdu and Bengali) [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk).

## Appendix 6

# Eular Response Criteria

Chart to review level of response

Current DAS28:	Current DAS:	Reduction of DAS28:		
		>1.2	>0.6 and ≤1.2	≤ 0.6
DAS28 ≤ 3.2	DAS ≤ 2.4	good	moderate	none
3.2 < DAS28 ≤ 5.1	2.4 < DAS28 ≤ 3.7	moderate	moderate	none
DAS28 > 5.1	DAS28 > 3.7	moderate	none	none

Van Gestel et al. Arthritis Rheum. 1998;41(10):1845-50.

## Appendix 7

# Business planning and resources

As a specialist practitioner, it is your responsibility to ensure that appropriate resources are available to provide safe and effective treatment in your unit. This appendix highlights resource issues to help you identify service needs in your area.

First, consider your current service and how well it reflects national provision or similar units' activity:

- ◆ how many patients do you see, on a weekly or annual basis?
- ◆ how efficient is your scheduling of appointments?
- ◆ what are the outcomes you measure to demonstrate satisfaction, efficiency, and performance indicators? Include patient reported outcome measures (PROMs)
- ◆ how accessible is the service for your population and is the locality able to serve the population well?
- ◆ is the service a cost effective one? How does your service compare to other services locally, regionally and nationally.

### Planning for better service provision

Planning for improved/sufficient service provision requires a clear and comprehensive understanding of the practical issues in treating patients with biologic therapies. You may need to review your services and prepare a business plan in conjunction with your managers and team.

Practitioners need to consider:

- ◆ number of patients who will receive a biologic therapy now and in the future. This will include a needs analysis based upon the patient population and unmet need/current provision
- ◆ proportion of treatment that will be administered via the subcutaneous or intravenous routes
- ◆ current therapies available, but also the future potential need to provide drug therapies pending licence
- ◆ figures which include year-on-year increases of patients each year continuing treatment, as well as those who will be receiving the drug therapy for the first time
- ◆ health policy and implications for potential changes in service delivery e.g. reduction in in-patient bed quotas

- ◆ an analysis of the ongoing follow-up service requirements for patients receiving biologic therapies and reviews (as pre-defined by NICE or other regulatory criteria). In some units, follow-up care is provided in the community (and by external home care services)
- ◆ the limitations or otherwise of current resources, including outpatient facilities and day care units
- ◆ the specialist staff skill mix required to deliver an effective service. Ensure adequate medical support is considered
- ◆ the equipment needs to deliver an effective service
- ◆ an economic analysis which includes the costs related to delivering treatment in the current service.

Note that if you are planning services which include the care of children and young people, you should refer to *Part 2: Children and young people* (page 34), which highlights particular issues for this patient group.

### Preparing your plan

In your plan, outline your planning considerations and set out the future resource requirements in the context of the local population needs. Then set out the practical aspects of delivering the service: include how the service will be routinely monitored and evaluated. Factors to consider for inclusion are set out below and include:

- ◆ an outline of the service
- ◆ the commissioning process and service re-design.

### An introduction to and outline of the service

#### Highlight:

- ◆ the patient population in your area currently receiving treatment, and those eligible but not currently receiving treatments (including predictions about demand in future years)
- ◆ calculations which predict how effective your unit could be in patient turnover and staffing levels, and outline the potential long term resource savings in comparison with short term costs. This could include potential improvements in patient care and satisfaction, and in data collection for local and national audit

- ◆ the potential for improved quality of life for patients (e.g. opportunities to return to work). Demonstrate an improved patient journey with, if possible, a reduction in what might be termed unnecessary visits. Highlight any potential cost savings directly to the unit or to the organisation. Refer to research evidence demonstrating reduction in joint erosions following treatment with biologics and emphasise the potential reduction in hospital admissions (e.g. for orthopaedic surgery and co-morbidity), requests for urgent outpatient appointments and associated social care costs
- ◆ the need for local audit
- ◆ risk management issues and factors that will help you manage risk.

It is also important to refer to:

- ◆ national guidelines such as NICE Guidance, where relevant in the UK
- ◆ details of the BSRBR, and the time implications involved in data collection for it.

### **Include practical data on providing the service**

For example:

- ◆ the number of infusions given before a patient's treatment is reviewed, frequency of treatments once established, the approximate number of episodes to train one patient in subcutaneous self-administration
- ◆ practitioners' time in the assessment, administration and monitoring of patients. It can be useful to demonstrate practitioner time per patient
- ◆ training costs for computer skills, venepuncture, cannulation or educating/teaching patients in subcutaneous administration skills
- ◆ screening costs, including pathology, radiology and TB screening, plus specialist support in interpreting tests and managing TB treatment
- ◆ equipment costs, including infusion pumps, infusion chairs or access to beds during the infusion, dressing packs and equipment for use during training for self administered subcutaneous injection
- ◆ facilities costs, including clinic space for assessment and review, and treatment space for training or administration, and resuscitation support
- ◆ specialist personnel needs and costs in the provision of specialist practitioner expertise to ensure effective and safe practice. This will vary according

to the service available, such as outpatient and day unit facilities. Consider training or supervision time and how to optimise the nursing resource depending on your team's skill mix and expertise in managing these patients

- ◆ clerical and administrative support needs, as well as information technology provision, to ensure high quality care, as well as good local data collection and BSRBR data.

### **Commissioning process and service re-design**

There are important principles that you should understand to ensure sustained provision of services. It is vital the current service providers are aware of how commissioning works and key factors that may affect the future provision and funding of services.

### **World Class Commissioning**

World Class Commissioning (WCC) is the term currently used in the NHS to describe the improved processes to enhance the commissioning process. It is important that you justify both activity and efficiency when developing your business case. Remember that quality and benefits to patients are equally as important as cost and value for money – although the focus will vary depending upon the organisation's financial status at the time of your submission.

WCC defines 11 competences. These competences are important factors to consider when providing evidence to justify your business proposal, as these will be indicators that the commissioners will be looking for. They are defined as:

- ◆ engaging with local communities
- ◆ working with clinicians
- ◆ developing partnerships
- ◆ needs assessment
- ◆ improving outcomes
- ◆ promoting innovation.

Information on WCC can be accessed via the Department of Health website:

[www.dh.gov.uk/en/Managingyourorganisation/Commissioning/Worldclasscommissioning/DH\\_](http://www.dh.gov.uk/en/Managingyourorganisation/Commissioning/Worldclasscommissioning/DH_)

### **Service re-design**

If you are trying to change services to fit the workload and centre them around patient need, you will need to assess your service for what works and what doesn't.

There are a number of ways of doing this including:

- ◆ mapping the patient journey
- ◆ highlighting gaps, bottlenecks and noting areas to improve efficiency
- ◆ looking at the co-ordination of the service with key stakeholders throughout the patient's pathway of care.

Innovation in services must include clinician and patient involvement, together with primary care trusts. Service design should consider pathways of care based on a detailed service specification which is cost effective and designed to meet local need. The major driver of these changes is the need to implement care closer to home: as a result, some of the biggest changes have been for primary care professionals who are taking on a variety of new roles in order to make better use of their skills.

For a greater understanding of the commissioning process and practice-based commissioning, see the Service redesign section in Appendix 13 (page 68).

### Wales (block grants)

In Wales, finances are negotiated from Westminster (via the Welsh Assembly), local health boards exist as key distributors of finance to NHS trusts with the proviso of long term service agreements to ensure standards and adherence to budgets. Funding is generally broken down into three main streams, hospitals and community services; GPs; and drug expenditure (NHS Wales, 2005).

### Scotland (community health partnerships)

In Scotland, community health partnerships, established from NHS boards, are pivotal in the re-design of services, providing opportunities to bring together clinicians, patients and public and other key stakeholders in order to improve care (NHS Scotland, 2007). These partnerships are aimed at shifting the balance to drive local community care.

### Northern Ireland (area boards)

The four Health Boards were abolished from 1 April 2009 and replaced with a single Regional Health and Social Care Board along with five local Commissioning Groups. They will focus on commissioning resource and performance management improvement.

## Appendix 8

# Classification of juvenile idiopathic arthritis (JIA)

**1. Oligoarticular onset:** less than five joints involved in the first six months of disease.

- ◆ Persistent: four or fewer total joints involved in the duration of follow up.
- ◆ Extended: five or more joints involved in the duration of follow up.

**2. Polyarticular onset:** five or more joints involved in the first six months of disease, usually involving small joints in a symmetrical distribution.

Rheumatoid Factor Positive

Rheumatoid Factor Negative

**3. Systemic onset:** chronic arthritis associated with systemic features. Including; high temperature, intermittent (quotidian) fever, evanescent (intermittent) transient episodic erythematous rash, lymphadenopathy and hepatosplenomegaly and serositis.

**4. Psoriatic arthritis:** chronic arthritis usually with asymmetrical small and large joint involvement and either evidence of psoriatic (including nail pits onycholysis) or family history of psoriasis in a first degree relative.

**5. Entesitis-related arthritis:** previously known as juvenile spondyloarthritis. Chronic arthritis associated with entesitis (inflammation at the insertion of tendons to the bone), with lower axial skeletal involvement. This subtype is strongly associated with HLA B27 and is more common in boys over six years.

**6. Unclassified:** any form of idiopathic chronic arthritis which does not fit into the above categories.

## Appendix 9

# BSPAR Guidelines for prescribing biologic therapies in children and young people with JIA

Taken from the BSPAR (formerly British Paediatric Rheumatology Group) *Guidelines for prescribing biologic therapies in children and young persons with juvenile idiopathic arthritis* (BPRG, 2002).

### Eligibility for treatment with etanercept in children and young people

(BPRG April 12th 2002)

#### Inclusion criteria

JIA of the following types:

- ◆ systemic
- ◆ polyarticular (sero-negative or positive for rheumatoid factor)
- ◆ extended oligo-articular
- ◆ psoriatic
- ◆ enthesitis-related.

And the following features:

- ◆ five or more swollen joints
- ◆ three or more joints with limitation of motion and pain, tenderness or both.

The measurement of disease activity must be strictly defined, objective and robust.

The standard core set data will be used to assess response to therapy:

- ◆ number of active joints
- ◆ number of joints with loss of range of movement
- ◆ physicians global assessment
- ◆ patient or parents global assessment
- ◆ Childhood Health Assessment Questionnaire
- ◆ ESR.

Measurements should be made at two points one month apart.

(For information on Varicella please see Appendix 10)

#### Failure of standard therapy

Patients must have had an adequate therapeutic trial of MTX. An adequate therapeutic trial would be defined as:

- ◆ treatment for at least three months at a dosage of parenteral MTX of 15 mg/m<sup>2</sup> weekly (unless significant toxicity limited the dose tolerated)
- ◆ ≥5 active joints and ≥3 joints with loss of motion plus pain/tenderness
- ◆ the disease is only controlled by unacceptable side effects of high doses of corticosteroids (>0.25 mg/kg daily) and has active disease as defined above in the last six months.

#### Exclusion criteria

Reference should be made to the drug data sheet (SPC), but important exclusions include:

- ◆ young women who are pregnant or breast feeding or who are sexually active without adequate contraception
- ◆ any infection
- ◆ current or previous TB
- ◆ previous or present sepsis of a prosthetic joint still in situ
- ◆ malignancy or pre-malignancy states
- ◆ immuno-deficiency.

#### Criteria for withdrawal of therapy

Treatment will be withdrawn in the event of adverse events:

- ◆ malignancy
- ◆ severe drug related toxicity

- ◆ pregnancy (temporary withdrawal)
- ◆ severe inter-current infection (temporary withdrawal).

Response should be assessed at six months core set outcomes and reference made to the current guidelines on continuing treatment.

### **Prescribing centres**

It is recommended that paediatric consultants or paediatricians/rheumatologists with appropriate training should only prescribe etanercept if they regularly see children and young people with JIA. They must have expertise in the use of parenteral MTX at the dosage described in this guidance. They must also be willing to take part in future studies of biologic agents. In addition, the centre must have a nurse specialist who is able to teach children and parents injection techniques and does this regularly. A condition of the drug licence is that all patients should be entered into the BPRG Biologic Registry. This reflects good practice for novel therapy.

This guidance will be reviewed in line with development of the BNDR.

## Appendix 10

# Testing for varicella antibodies in children

All patients should have their varicella antibody status measured at diagnosis and certainly before commencing immuno-suppressive treatment (including etanercept, steroids and MTX).

In children and young people who do not have adequate antibodies, this test should be re-checked annually as the child/young person may have been in contact with chicken pox and sero-converted to being positive.

If it is possible to delay commencement of immuno-suppressive therapy, children/young people should be considered for varicella immunisation, if appropriate prior to starting immuno-suppressive therapy. This does not always give full immunity and may need to be repeated. If siblings have not had chicken pox they too should be considered for vaccination.

There are three issues to consider when immuno-suppressing children and young people following the administration of a live vaccine:

1. the risk of clinically developing the illness from the vaccine
2. the immune response being modified such that the vaccine will be less effective
3. the timing of the commencement of treatment should be discussed with the prescribing physician.

Zoster immunoglobulin (ZIG) can be given to a sero-negative patient who has been in contact with chicken pox if given less than 72 hours from contact (it may attenuate infection if given up to 10 days post exposure). However, this will only provide temporary immunity of approximately four weeks.

Acyclovir prophylaxis should be considered, if there has been close contact with someone who has chicken pox by a child/young person who does not have known immunity to chicken pox. Intravenous acyclovir can be given if a child/young person displays clinical features of chicken pox (RCPCH, 2002). If either of the above situations occur, families should be advised to contact their rheumatology team or GP immediately.

All live vaccines are contra-indicated, for example oral polio, BCG, MMR, oral typhoid and yellow fever vaccines.

Flu and pneumovax vaccines are recommended in immuno-compromised patients.

When a vaccination is administered, it is important that this information is communicated to the multi-disciplinary and primary care teams.

## Appendix 11

# The RCN Rheumatology Biologics Working Parties

## Members of the RCN Rheumatology Biologics Working Party

### Representation

All the members of the Arthritis Musculoskeletal Alliance (ARMA) were involved in the development of this guidance:

- ◆ Arthritis Care
- ◆ Arthritis and Musculoskeletal Alliance (ARMA)
- ◆ British Healthcare Professionals Allied to Rheumatology
- ◆ British Society of Paediatric and Adolescent Rheumatology (BSPAR – nursing, medicine and allied healthcare professionals)
- ◆ British Society for Rheumatology (clinical affairs committee)
- ◆ National Rheumatoid Arthritis Society (NRAS)
- ◆ Royal College of Nursing Rheumatology Forum.

### Members

#### Principal author and Working Party Lead

Susan Oliver RGN MSc FRCN.

Working Party Co-ordinator and member of the RCN Policy and Practice Rheumatology Forum, and Chief Nurse Adviser for the National Rheumatoid Arthritis Society (NRAS).

Nurse Consultant Rheumatology, Southampton University Hospital NHS Trust & Litchdon Medical Centre, Barnstaple, Devon. Telephone: 01271 374294

Email: sue@susanoliver.com

#### Working Party Members

Shane Artis, Principal Pharmacist, Community Hospitals, Stoke-on-Trent Community Health Services, hosted by NHS Stoke-on-Trent.

Ailsa Bosworth, Chief Executive & Patient Representative National Rheumatoid Arthritis Society, Berks.

Sue Brown MSc RGN, Specialist Nurse, Royal National Hospital for Rheumatic Diseases, Bath.

Maggie Carr RGN DPSN MSc, Nurse Consultant in Rheumatology, St. Peter's Chertsey, Surrey.

Maureen Cox RGN MSc Dip N ONC, Clinical Nurse Specialist, Nuffield Orthopaedic Centre, NHS Trust Oxford.

Trish Cornell RGN, Rheumatology Advanced Nurse Practitioner, Poole Hospital, Dorset. Also representing BHPR.

Dr. Christopher Deighton MD FRCP, Consultant Rheumatologist, Special Lecturer, Derbyshire Royal Infirmary.

Jane Dunnage, Chair Lupus UK.

Kate Gadsby BSc RGN, Rheumatology Nurse Specialist and Lead Clinical Educator, Derby Royal Infirmary, Derby.

Sheena Hennell MSc RGN, Nurse Consultant, Arrows Park Hospital.

Diane Home MSc RGN, Nurse Consultant West Middlesex Hospital, London.

Dawn Homer MSc, Nurse Consultant, Selly Oak Hospital, Birmingham.

Kate Llewellyn, Head of Information, representing Arthritis Care, London.

Professor D.G. I. Scott MD FRCP, Consultant Rheumatologist & Honorary Professor of Rheumatology, Chief Medical Adviser to the National Rheumatoid Arthritis Society, Patient Involvement Officer Royal College of Physicians, Norfolk & Norwich University Hospital, Norfolk.

Jane Skerrett, Director National Ankylosing Spondylitis Society.

Hannah Vernon, Patient Representative National Ankylosing Spondylitis Society. [www.nass.co.uk](http://www.nass.co.uk).

Nicola Waldron MSc RGN, Nurse Specialist, Royal National Hospital for Rheumatic Diseases NHS Trust.

Janet Williams, Nurse Specialist and Jacqueline Novak  
Advanced Nurse Practitioner, St. Helen's Hospital,  
Merseyside.

### **Representing Scotland**

E. McIvor RGN MSc, Clinical Nurse Specialist.

### **Representing Northern Ireland**

Elaine Wylie RGN BSc (Hons) PGDip, Rheumatology  
Nurse Specialist, Craigavon Hospital.

### **Representing Wales**

Lisa Howie, Clinical Nurse Specialist.

## **Paediatric Working Party**

### **Lead Author**

Liz Hutchinson MSc RSCN RGN DN Cert, Paediatric  
Rheumatology Clinical Specialist Nurse, Queen's  
Medical Centre, Nottingham University Hospital NHS  
Trust, Nottingham.

### **Members of paediatric working group**

Pam Whitworth RGN RSCN, Paediatric Rheumatology  
Clinical Nurse Specialist, Birmingham Children's  
Hospital.

Dr. Gavin Cleary, Consultant Rheumatologist & BSPAR  
convenor Alder Hey Children's Hospital NHS  
Foundation Trust, Liverpool.

Caroline Jess, Rheumatology Day Unit Manager, Nuffield  
Orthopaedic Centre NHS Trust, Oxford.

### **South West:**

Julia Taylor, Rheumatology Nurse Practitioner, Poole  
Hospital NHS Foundation Trust, Poole, Dorset.

Samantha Carvalho, Rheumatology Nurse Specialist,  
Princess Elizabeth Hospital, Guernsey.

Sue Brown MSc RGN EN (G), Clinical Nurse Specialist in  
Connective Tissue Diseases, Royal National Hospital for  
Rheumatic Diseases NHS Foundation Trust.

### **North:**

Gill Wilson, Clinical Nurse Specialist in Rheumatology,  
Freeman Hospital, Newcastle upon Tyne.

Domini Bryer, Clinical Nurse Specialist & Team Leader-  
Biologics, Rheumatology Day Case Unit, Leeds Teaching  
Hospitals NHS Trust, Leeds.

### **London:**

Silvia Gracia, Rheumatology Clinical Nurse Specialist,  
Whittington Hospital, London.

### **Scotland:**

Ellen Forde, Rheumatology Nurse Specialist, Inverclyde  
Royal Hospital.

## **Acknowledgements**

### **With thanks for resources offered:**

The British Society for Rheumatology for sharing their  
draft documents in preparation for this guidance.

Derby Hospitals NHS Foundation Trust.

University Birmingham NHS Foundation Trust.

### **With thanks to our email reviewers:**

#### **South East:**

Nicky Kennedy, Nurse Specialist, Wexham Park  
Hospital, Slough.

Debbie Bond, Rheumatology Specialist Nurse, Queen  
Elizabeth Hospital, Kings Lynn, Norfolk.

## Appendix 12

# Grading of evidence

The RCN Rheumatology Biologics Working Party graded the evidence it used in preparing Part 1: Adult Patients following the grading system shown here.

The grade or level is listed next to the relevant references in the References: Part 1 Adult Patients on page 70.

Level of evidence	Type of evidence	Grade of recommendation
ia	Meta-analysis of randomised controlled trials. (RCTs)	A
ib	At least one RCT	A
iiia	At least one well designed controlled study but without randomisation	B
iiib	At least one well designed quasi-experimental design	B
iii	At least one non experimental descriptive study (e.g. comparative correlation or case study)	
iv	Expert committee reports, opinions and / or experience of respected authorities	C

## Appendix 13

# Websites and resources

### Arthritis Care

Arthritis Care offers practical and emotional support to help people learn to manage their condition more effectively, including guidance for adults and children receiving treatment with biologic drugs.

- ◆ Professional confidential helpline offering information and support: freephone 0808 800 4050 (weekdays 10am-4pm).  
Email: [helplines@arthritiscare.org.uk](mailto:helplines@arthritiscare.org.uk).
- ◆ The Source – Arthritis Care’s helpline for young people aged 25 and under. Freephone helpline 0808 808 2000 (weekdays 10am-4pm).  
Email: [thesource@arthritiscare.org.uk](mailto:thesource@arthritiscare.org.uk).
- ◆ Online discussion forums offer peer support and the opportunity to share experiences:  
[www.arthritiscare.org.uk/forums](http://www.arthritiscare.org.uk/forums).
- ◆ Write to: Arthritis Care, 18 Stephenson Way, London NW1 2HD.
- ◆ [www.arthritiscare.org.uk](http://www.arthritiscare.org.uk).

### Lupus UK

Lupus UK offers support and information to people with systemic lupus erythematosus, and funds research into the condition. It has a nationwide group of contacts who offer a listening ear to patients.

- ◆ Telephone 01708 731251 (9am – 5pm weekdays).
- ◆ Website (includes section for professional clinicians): [www.lupusuk.org.uk](http://www.lupusuk.org.uk).

### National Ankylosing Spondylitis Society (NASS)

NASS provides information and advice for people with AS who are on a biologic therapy or being considered for one. This covers eligibility, information on particular drugs and lifestyle issues. NASS can also put people in touch with others who are already taking a biologic therapy for reassurance and support. Specific medical questions are referred to those NASS trustees who are clinicians or to other health professionals.

- ◆ Contact NASS on 0208 948 9117.
- ◆ Email: [nass@nass.co.uk](mailto:nass@nass.co.uk).
- ◆ Website: [www.nass.co.uk](http://www.nass.co.uk).
- ◆ Write to: NASS, Unit 0.2, 1 Victoria Villas, Richmond, Surrey TW9 2GW.

### National Rheumatoid Arthritis Society (NRAS)

The NRAS helpline team is fully conversant with all patient issues relating to biologic therapies and can provide detailed, written information to callers on a variety of subjects, from eligibility criteria to individual drug details. The website also has information. There is a nationwide network of NRAS medical advisers who can answer specific, detailed medical queries. Patients can also speak to volunteers who are successfully benefitting from different biologic therapies, which can help reassure people about to start treatment.

- ◆ NRAS helpline: freephone 0800 298 7650, Monday to Friday, 9.30am – 4.30pm.
- ◆ Email: [enquiries@rheumatoid.org.uk](mailto:enquiries@rheumatoid.org.uk).
- ◆ Write to: NRAS, Unit B4 Westacott Business Centre, Westacott Way, Littlewick Green, Maidenhead, SL6 3RT.
- ◆ [www.rheumatoid.org.uk](http://www.rheumatoid.org.uk).

### NHS confederation

Member organisations can access publications at: [www.nhsconfed.org](http://www.nhsconfed.org).

### Psoriatic Arthropathy Alliance and the Psoriasis Support Trust (PAPAA)

PAPAA was formed in 2007 from two existing charities, the Psoriatic Arthropathy Alliance (PAA) and the Psoriasis Support Trust (PST). It aims to become a principle resource of information and help for people with psoriasis and psoriatic arthritis in the UK.

Website: [www.papaa.org](http://www.papaa.org)

### Patient information leaflets on Tuberculosis treatment

[www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)

### Royal College of Nursing Rheumatology Forum

[www.rcn.org.uk/rheumatology](http://www.rcn.org.uk/rheumatology)

The following documents are to be used in conjunction with this publication and are available to download from [www.rcn.org.uk/biologicsresources](http://www.rcn.org.uk/biologicsresources)

- ◆ *Proforma for rheumatology daycase Rituximab first infusion*, Southern Derbyshire Acute Hospitals NHS Trust
- ◆ *Protocol for administering subcutaneous methotrexate*, Selly Oak Hospital

- ◆ *Psoriatic joint sheet*, BSRBR
- ◆ DAS 28 joint assessment webcast
- ◆ *EULAR response criteria*, Professor Piet van Riel
- ◆ Example of PCT funding request form for treatment with biologics
- ◆ Examples of travel letters for biologics
- ◆ *Rituximab care pathway for rheumatoid arthritis*, The Rheumatology Department, Nuffield Orthopaedic Centre, Oxford
- ◆ *Algorithm for patients receiving intravenous biologic therapy*.

### Royal College of Paediatrics and Child Health

[www.rcpch.ac.uk](http://www.rcpch.ac.uk)

### Scottish Consensus Guidelines

[www.sign.ac.uk](http://www.sign.ac.uk)

### Summaries of Product Characteristics (SPCs)

[www.medicines.org.uk](http://www.medicines.org.uk)

### Service redesign

- ◆ Department of Health website, [www.dh.gov.uk](http://www.dh.gov.uk), for the document *Commissioning framework for health and wellbeing* (March 2007).
- ◆ Lord Darzi's Next Stage Review: The 2008 report on the NHS, available at: [www.ournhs.nhs.uk](http://www.ournhs.nhs.uk).
- ◆ NHS Institute: support for innovation and change within the NHS: [www.institute.nhs.uk](http://www.institute.nhs.uk).
- ◆ NICE commissioning guides to support service redesign in many specialties, at: [www.nice.org.uk](http://www.nice.org.uk).
- ◆ No Delays Achiever: website for guidance on writing a business case on service redesign and other useful resources, [www.nodelaysachiever.nhs.uk/ServiceImprovement/Tools/IT157\\_RoleRedesign.htm](http://www.nodelaysachiever.nhs.uk/ServiceImprovement/Tools/IT157_RoleRedesign.htm).
- ◆ RCN website, [www.rcn.org.uk](http://www.rcn.org.uk) where commissioning documents available include: *Commissioning a patient led NHS*; and *Commissioning health care services for children and young people*.
- ◆ Policy briefings on health reforms including guidance on commissioning.

### Patient information leaflets

Information leaflets for patients on biologics are provided at the following sites.

### Adults:

- ◆ Arthritis Care: [www.arthritiscare.org.uk](http://www.arthritiscare.org.uk)
- ◆ Arthritis Research Campaign: [www.arc.org.uk](http://www.arc.org.uk)
- ◆ Juvenile SLE group: [www.liv.ac.uk/ukjsle](http://www.liv.ac.uk/ukjsle)
- ◆ Lupus UK: [www.lupusuk.org.uk](http://www.lupusuk.org.uk)
- ◆ National Ankylosing Spondylitis Society: [www.nass.co.uk](http://www.nass.co.uk)
- ◆ National Rheumatoid Arthritis Society: [www.rheumatoid.org.uk](http://www.rheumatoid.org.uk)
- ◆ Psoriatic Arthritis: [www.paalliance.org](http://www.paalliance.org).

### Children and young people:

- ◆ Arthritis Care [www.arthritiscare.org.uk](http://www.arthritiscare.org.uk) (including living with arthritis/young people section: [www.arthritiscare.org.uk/LivingwithArthritis/Youngpeople](http://www.arthritiscare.org.uk/LivingwithArthritis/Youngpeople); and dedicated site for young people, The Source: [www.arthritiscare.org.uk/PublicationsandResources/AdviceLine/TheSource](http://www.arthritiscare.org.uk/PublicationsandResources/AdviceLine/TheSource))
- ◆ Arthritis Research Campaign: [www.arc.org.uk](http://www.arc.org.uk) (including: *Arthritis: A guide for teenagers*)
- ◆ Chat booklet for all parents, and Chat 2 booklet for parents of teenagers: [www.ccaa.org.uk](http://www.ccaa.org.uk)
- ◆ DREAM Team: Dedicated Rheumatology Expert Adolescent Multi-disciplinary Team (resources for young people with conditions like arthritis, their families and professionals): [www.dreantean-uk.org/index.php?main](http://www.dreantean-uk.org/index.php?main)
- ◆ Kids with Arthritis: [www.kidswitharthritis.org](http://www.kidswitharthritis.org)
- ◆ Lupus Society: [www.lupus.org.uk](http://www.lupus.org.uk)
- ◆ National Ankylosing Spondylitis Society: [www.nass.co.uk](http://www.nass.co.uk)
- ◆ National Rheumatoid Arthritis Society: [www.rheumatoid.org.uk](http://www.rheumatoid.org.uk)
- ◆ Paediatric Rheumatology International Trials Organisation: [www.pediatric-rheumatology.printo.it](http://www.pediatric-rheumatology.printo.it)
- ◆ Patient held record: [www.sickkids.on.ca/myhealthpassport](http://www.sickkids.on.ca/myhealthpassport)
- ◆ Royal College of Paediatrics and Child Health (RCPCH) – many drugs used to treat children and young people are unlicensed. RCPCH has a leaflet giving guidance on the use of these: [www.rcpch.org.uk](http://www.rcpch.org.uk).

# References

## Part 1: Adult patients

### References

**Note: The RCN Rheumatology Biologics Working Party's grades of recommendation or levels of evidence are included after the document where relevant.**

Alonso-Ruiz A, Pijoan J, Ansuategui E, Urkaregi A, Calabozo M and Quintana A (2008) Tumour necrosis factor alpha drugs in rheumatoid arthritis; a systematic review and meta analysis of efficacy and safety, *BMC Musculoskeletal Disorders*, 9, pp.52-79. **LEVEL OF EVIDENCE IA.**

Baildman E and Davidson J (2008) BSPAR position statement on professionals working in paediatric rheumatology, *Rheumatology*, 47, pp.743-744. **GRADE OF RECOMMENDATION A-C.**

British Paediatric Rheumatology Group (2000) *Guidelines for prescribing biologic therapies in children and young people with juvenile idiopathic arthritis*, British Paediatric Rheumatology Group: London. **GRADE OF RECOMMENDATION A-C.**

British Society for Rheumatology (2002) *Guidelines on immunisation and screening for immuno-compromised patients*, BSR.

British Society for Rheumatology Clinical Affairs Committee and Standards Audit and Guidelines Working Group (2009) *Rheumatoid Arthritis Biologics Guidelines*, BSR. **GRADE OF RECOMMENDATION C.**

British Thoracic Society Standards of Care Committee (2005) British Thoracic Society recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti TNF $\alpha$  treatment, *Thorax*, 44 (60), pp.800-805. **GRADE OF RECOMMENDATION A-C.**

BSR Clinical Affairs Committee and Standards, Audit and Guidelines Working Group (2009) British Society for Rheumatology Rheumatoid Arthritis Biologics Guidelines, (pending publication).

Carr AJ (2001) *Defining the extended clinical role for allied health professionals in rheumatology*, Arthritis Campaign: Conference Proceedings, (12) Arthritis Research Campaign, Derbyshire.

Chakravarety K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, Mooney J, Somerville M and

Bosworth A on behalf of British Society for Rheumatology and British Health Professionals in Rheumatology Standard, Guidelines and Audit Working Group in association with the British Association of Dermatology (2006) BSR and BHPR guidelines for disease modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists, *Rheumatology*, 47 (6), pp.924-925. Accessible from <http://rheumatology.oxfordjournals.org/cgi/data/kel216a/DC1/1>. **GRADE OF RECOMMENDATION A-C.**

Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L and Plevy S (2003) The incidence and management of infusion reactions to infliximab: a large centre experience, *The American Journal of Rheumatology*, 98 (6) pp.1315-1324. **LEVEL OF EVIDENCE III.**

Cohen S, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hesse EW, and Shaw T, Totoritis MC for the Reflex Trial Group (2006) Rituximab for rheumatoid arthritis refractory to anti-tumour necrosis factor therapy, *Arthritis & Rheumatism*, 54 (9) pp.2793-2806.

Department of Health (2006) *The Green Book 2006*, London: Stationery Office.

Department of Health (2007) *World Class Commissioning*, London: DH.

Department of Health (2007) *Practice Based Commissioning*, London: DH.

Dixon W, Hyrich K, Watson K, and Lunt M (2008) Drug specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the BSR biologics register BSRBR Rheumatology, *Rheumatology*, 47 (2). **LEVEL OF EVIDENCE IIB.**

Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, and British Society for Rheumatology Biologics Register Control Centre, Consortium and AJ Silman on behalf of the BSR Biologics Register (2007) Serious infection following anti-tumour necrosis factor alpha therapy in patients with rheumatoid arthritis, *Arthritis & Rheumatism*, 56 (9) pp.2896-2904. **GRADE OF RECOMMENDATION B.**

Dougherty L and Lister S (editors) (2009) *The Royal Marsden Hospital Manual of Clinical Nursing Procedures* (6th edition), Blackwell Publishing: Oxford.

Drugs and Therapeutic Bulletin (2008) Rituximab and abatacept for rheumatoid arthritis in adults, *Drugs and Therapeutic Bulletin*, 46, pp.57-61.

Emery P, Keystone E, Tony H, Cantagrel A, van Vollenhoven R, Sanchez A, Alecock E, Lee J and Kremer J (2008) IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF $\alpha$  biologics; results from a 24 week multicentre randomised placebo controlled trial, *Annals of Rheumatic Diseases*, 67 (11), pp.1516-1523. **LEVEL OF EVIDENCE IB.**

Furst D, Keystone E, Kirkham B, Fleischmann R, Mease P, Breedveld F, Smolen F, Kalden J, Burmester G, Braun J, Emery P, Winthrop K, Bresnihan B, De Benedetti F, Dörner T, Gibofsky A, Schiff M, Sieper J, Singer N, Van Riel P, Weinblatt M and Weisman M (2008) Updated consensus statement on biologic agents for the treatment of rheumatic diseases, *Annals of Rheumatic Diseases*, 67, Supp III iii2-iii25. **GRADE OF RECOMMENDATION A-C.**

Gomez-Reino JJ, Carmona L, Angel, and Descalzo M (2007) Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection, *Arthritis & Rheumatism*, 57, pp.756-761.

Hiley J, Homer D, and Clifford C (2008) Patient self-injection of methotrexate for inflammatory arthritis: A study evaluation the introduction of a new type of syringe and exploring patients' sense of empowerment, *Musculoskeletal Care*, 6 (1) pp.15-30.

**LEVEL OF EVIDENCE III.**

Hyrich KL, Watson KD, Silman AJ, Symmons DPM, and the BSR Biologics Register (2006) Predictors of response to anti-TNF $\alpha$  therapy among patients with rheumatoid arthritis; results from the British Society for Rheumatology Biologics Register, *Rheumatology*, 45, pp.1558-1565.

Kapetanovic M, Saxne T, Sjöholm A, Truedsson L, Jönsson G and Geborek P (2006) Influence of methotrexate, TNF blockers and prednisolone on antibody response to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis, *Rheumatology*, 46 (106) pp.608-611. **LEVEL OF EVIDENCE IA.**

Kay J, Matteson E, Dasgupta B, Nash P, Durez P, Hall S, Hsia E, Han J, Wagner C, Xu Z, Visvanathan S and Rahman M (2008) Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate, *Arthritis and Rheumatism*, 58 (4), pp.964-975. **LEVEL OF EVIDENCE IIB.**

Keat A, Barkham N, and Bhalla A on behalf of the BSR Standards, Guidelines and Audit Working Group (2005) BSR guidelines for prescribing TNF $\alpha$  blockers in adults with ankylosing spondylitis. Report of the working party of the British Society for Rheumatology, *Rheumatology*, 44, pp.939-947. **GRADE OF RECOMMENDATION A-C.**

Kyle S, Chandler D, Griffiths C, Helliwell P, Lewis J, McInnes I, Oliver S, Symmons D and McHugh N on behalf of the British Society for Rheumatology Standards Guidelines Audit Working Group (2005) Guidelines for anti-TNF $\alpha$  therapy in psoriatic arthritis, *Rheumatology*, 44 (3) pp.390-397. **GRADE OF RECOMMENDATION A-C.**

Maini R, Taylor P, Szechinski J, Pavelka K, Bröll J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D and Kishimoto T for the Charisma Study Group (2006) Double blind randomised controlled clinical trial of the interleukin 6 receptor antagonist tocilizumab in European patients with rheumatoid arthritis who had an incomplete response to methotrexate, *Arthritis & Rheumatism*, 54 (9), pp.2817-2829. **LEVEL OF EVIDENCE IB.**

Moore RA, Derry S, and McQuay H and Paling J (2008) What do we know about communicating risk? A brief review of suggestion for contextualising serious, but rare, risk and the example of cox-2 selective and non-selective NSAIDs, *Arthritis Research & Therapy*, 10, R20.

National Institute of Clinical Excellence (2003) *Anakinra for rheumatoid arthritis*, London: NICE.

National Institute of Clinical Excellence (2007a) *Rituximab for the treatment of rheumatoid arthritis Single technology appraisal 126*, London: NICE.

National Institute of Clinical Excellence (2007b) *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis Guidance 36*, London: NICE.

National Institute of Clinical Excellence (2008a) *Abatacept for the treatment of rheumatoid arthritis Single technology appraisal 141*, London: NICE.

National Institute of Clinical Excellence (2008b) *Adalimumab, etanercept, infliximab for ankylosing spondylitis Guidance 143*, London: NICE.

National Institute of Clinical Excellence (2008c) *Etanercept and infliximab for the treatment of psoriatic arthritis Guidance 104*, London: NICE.

National Institute of Health and Clinical Excellence (2009) *Guideline for RA management*, London: NICE. **GRADE OF RECOMMENDATION A-C**

- NHS Wales (2005) *NHS Wales funding and legislation*. Accessible from [www.wales.nhs.uk/site3](http://www.wales.nhs.uk/site3).
- Nursing and Midwifery Council (2004) *Guidelines for the administration of medicines*, London: NMC.
- Nursing and Midwifery Council (2005) *Guidelines for records and records keeping*, London: NMC.
- Nursing and Midwifery Council (2007) *Standards for medicines management*, London: NMC.
- Nursing and Midwifery Council (2008) *Standards of conduct, performance and ethics for nurses and midwives*, London: NMC.
- O'Connor A, Rostom A, and Fiset V (1999) Decision aids for patients facing health treatment or screening decisions. A Cochrane systematic review, *British Medical Journal*, 319, pp.731-734.
- Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, Comaneshter D, Levartovsky D, Mendelson E, Azar R, Wigler I, Balbir-Gurman A, Caspi D and Elkayam O. (2008) Vaccination against influenza in patients with rheumatoid arthritis; the effect of rituximab on the humoral response, *Annals of Rheumatoid Disease*, 67, pp.937-941. **LEVEL OF EVIDENCE IA.**
- Parliament (2005) *The Mental Capacity Act 2005* [Chapter 9], London: The Stationery Office.
- Parliament (2007) *The Mental Capacity Act 2007*, [Chapter 9], London: The Stationery Office.
- Royal College of Nursing (2003) *Standards of infusion therapy*, London: RCN.
- Royal College of Nursing (2004) *Administering subcutaneous methotrexate for inflammatory arthritis*, London: RCN.
- Royal College of Nursing (2005) *Dermatology Practical competencies*, London: RCN.
- Royal College of Nursing (2007a) *Standards for infusion therapy*, London: RCN.
- Royal College of Nursing (2007b) *Telephone advice line for people with long term conditions*, London: RCN.
- Royal College of Nursing (2008) *Advance nurse practitioner guide to competencies and programme accreditation*, London: RCN.
- Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Almazor MS, Bridges LS, Chatham WW, Hochberg M, Maclean C, Mikulus T, Moreland LW, O'Dell J, Turkiewicz AM, and Furst DE (2008) American College of Rheumatology recommendations for the use of nonbiologic and biologic disease modifying anti-rheumatic drugs in rheumatoid arthritis, *Arthritis & Rheumatism*, 59 (6), pp.762-784. **GRADE OF RECOMMENDATION A-C.**
- The Scottish Government (2007) *Better health, better care, action plan*, Edinburgh: The Stationery Office.
- Smitten AL, Simon TA and Hochberg MC and Suissa S (2008) A meta analysis of the incidence of malignancy in adult patients with rheumatoid arthritis, *Arthritis Research & Therapy*, 10, R45. **LEVEL OF EVIDENCE IA.**
- Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester GR, Dougados M, Ferraccioli G, Jaeger U, Klareskog L, Kvien TK, Martin-Mola E, Pavelka K, and The Working Group on the Rituximab consensus statement (2007) Consensus statement on the use of rituximab in patients with rheumatoid arthritis, *Annals of Rheumatic Diseases*, 66, pp.143-150. **GRADE OF RECOMMENDATION A-C.**

## References

### Part 2: Children and young people

- Abbott Laboratories Limited (September 2008) *Summary of Product Characteristics*. Abbott.
- British Society of Paediatric and Adolescent Rheumatology (BSPAR) (2007) *Position statement on professionals working in paediatric rheumatology*. Available at [www.bspar.org.uk](http://www.bspar.org.uk).
- British Society of Paediatric and Adolescent Rheumatology (BSPAR) (2009) *Standards of care*. Available on BSPAR website [www.bspar.org.uk](http://www.bspar.org.uk).
- Department of Health (2004) *National Service Framework for children, young people and maternity services – Every Child Matters*, London: The Stationery Office. Available at [www.dh.gov.uk](http://www.dh.gov.uk).
- Department of Health (2006) *The Green Book 2006*, London: The Stationery Office.
- Horneff G, De Bock F, Foeldvari I, Girschick H, Michels H, Moebius D and Schmelting H (2008) Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry, *Annals of the Rheumatic Diseases*, 68, pp.519-525.
- Lovell DJ, Gianni EH, Reiff A, Cawkell GD (2000) Etanercept in children with polyarticular juvenile rheumatoid arthritis, *New England Journal of Medicine*, 342, pp.763-9 (A).
- Lovell D, Giannini E, Reiff A, Jones O, Schneider R, Olson J, Stein L, Gedalia A, Ilowite N, Wallace C, Lange M, Finck B and Burge D (2003) Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Interim results from an ongoing multi-centre, open-label, extended-treatment trial, *Arthritis and Rheumatism*, 48 (1), pp218-226.
- Lovell D, Reiff A, Ilowite N, Wallace C, Chon Y, Lin S, Baumgartner S and Giannini E (2008) Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis, *Arthritis & Rheumatism*, 53 (5), pp.1496-1504.
- Lovell D, Ruperto N, Goodman S, Reiff A, Martini A, Giannini E, Radin A, Rao V and Spencer-Green G (2004) Preliminary data from the study of adalimumab in children with JIA, arthritis and rheumatism, *J Rheumatol*, 31 pp.179-182.
- Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe R, Weiner L, Horneff G, Huppertz H, Olson N, Medich J, Carcereri-De-Prati R, McIlraith M, Giannini E and Martini A, Pediatric Rheumatology Collaborative Study Group, Pediatric Rheumatology International Trials Organisation (2008) Adalimumab with or without methotrexate in juvenile rheumatoid arthritis, *New England Journal of Medicine*, 359 (8), pp.10-20.
- National Institute for Clinical Excellence (2002a) *Patient information: guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis*, London: NICE. Available at [www.nice.org.uk](http://www.nice.org.uk).
- National Institute for Clinical Excellence (2002b) *Patient information: Guidance on the treatment of juvenile idiopathic arthritis*, London: NICE. Available at [www.nice.org.uk](http://www.nice.org.uk).
- National Institute for Clinical Excellence (2002c) *Guidance on the use of etanercept for juvenile idiopathic arthritis: Technology Appraisal No. 35A*, London: NICE. Available at [www.nice.org.uk](http://www.nice.org.uk).
- Nursing and Midwifery Council (1997) *Working in posts not related to your registration*, London: NMC. Available at [www.nmc-uk.org](http://www.nmc-uk.org).
- Nursing and Midwifery Council (2007) *Statement of interprofessional values underpinning work with children and young people*, London: NMC. Available at [www.nmc-uk.org](http://www.nmc-uk.org).
- Nursing and Midwifery Council (2008a) *Advice for people working with children and young people*, London: NMC. Available at [www.nmc-uk.org](http://www.nmc-uk.org).
- Nursing and Midwifery Council (2008b) *The Code: Standards of conduct, performance and ethics for nurses and midwives*, London: NMC. Available at [www.nmc-uk.org](http://www.nmc-uk.org).
- Petty R, Southwood T, Manners P, Baum J, Glass D, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur A, Suarez-Almazor M, Woo P and International League of Associations for Rheumatology (2004) International League of Associations for Rheumatology Classification of juvenile idiopathic arthritis second revision, Edmonton 2001, *Rheumatology*, 31, pp.390-392.

Royal College of Paediatrics and Child Health (2000) *Medicines for children: important information for parents and carers*, London: RCPCH. Available at [www.rcpch.org.uk](http://www.rcpch.org.uk).

Royal College of Paediatrics and Child Health (2002) *Immunisation of the immuno-compromised patient: best practice statement*, London: RCPCH. Available at [www.rcpch.org.uk](http://www.rcpch.org.uk).

The British Paediatric Rheumatology Group (2000) *Guidelines for prescribing biologic therapies in children and young people with juvenile idiopathic arthritis*, London: BSPAR. Available at [www.bspar.org.uk](http://www.bspar.org.uk).

Royal College of Nursing (2008) *Competencies: and integrated career and competency framework for paediatric endocrine nurse specialists*, London: RCN.

## Further reading

Hutchinson L and Strike H (2006) *Juvenile Idiopathic Arthritis (JIA) Oxford Handbook for Children and Young People's Nursing*, Oxford University Press: Oxford.

Jackson G (2006) *Paediatric Rheumatology, Rheumatology Nursing – A Creative Approach* (2nd edition), Wiley: London.

Royal College of Nursing (2002) *Position statement on injection technique*, London: RCN. Available at [www.rcn.org.uk](http://www.rcn.org.uk).

Royal College of Nursing (2002) *Caring for young people: Guidance for nursing staff*, London: RCN. Available at [www.rcn.org.uk](http://www.rcn.org.uk).

Royal College of Nursing (2004) *Subcutaneous methotrexate in inflammatory arthritis*, London: RCN. Available at [www.rcn.org.uk](http://www.rcn.org.uk).

Workman B. (1999) Safe injection technique, *Nursing Standard*, 13 (39), June 16, pp.47-53.

### RCN Legal Disclaimer

This publication contains information, advice and guidance to help members of the RCN. It is intended for use within the UK but readers are advised that practices may vary in each country and outside the UK.

The information in this publication has been compiled from professional sources, but its accuracy is not guaranteed. Whilst every effort has been made to ensure the RCN provides accurate and expert information and guidance, it is impossible to predict all the circumstances in which it may be used. Accordingly, to the extent permitted by law, the RCN shall not be liable to any person or entity with respect to any loss or damage caused or alleged to be caused directly or indirectly by what is contained in or left out of this information and guidance.

Published by the Royal College of Nursing, 20 Cavendish Square, London, W1G 0RN

© 2009 Royal College of Nursing. All rights reserved. Other than as permitted by law no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise, without prior permission of the Publishers or a licence permitting restricted copying issued by the Copyright Licensing Agency, Saffron House, 6-10 Kirby Street, London EC1N 8TS. This publication may not be lent, resold, hired out or otherwise disposed of by ways of trade in any form of binding or cover other than that in which it is published, without the prior consent of the Publishers.



The RCN represents nurses and nursing, promotes excellence in practice and shapes health policies.

**October 2009, second edition**

RCN Online  
[www.rcn.org.uk](http://www.rcn.org.uk)

RCN Direct  
[www.rcn.org.uk/direct](http://www.rcn.org.uk/direct)

0345 772 6100

Published by the  
Royal College of Nursing  
20 Cavendish Square  
London  
W1G 0RN

020 7409 3333

Publication code 001 984

ISBN: 978-1-906633-13-4

Sponsorship was received from the following pharmaceutical companies:



The monies received were used in the development, publication and distribution of this guidance by the RCN. The sponsoring companies had no editorial control over or input into this guidance except to review the guidance for factual accuracy. The views and opinions contained in this guidance are those of the authors and not necessarily those of the sponsoring companies.