High Cost Drugs Pathway for Rheumatoid Arthritis

July 2017

Version 4 (This supersedes version 3)

Review due July 2019

Authors

Meghna Jani¹, Vanessa Reid², Ben Parker³, Sarah Jacobs⁴, Hector Chinoy⁵, Ian Bruce⁶

¹ NIHR Clinical Lecturer in Rheumatology, University of Manchester/ CMFT, UK
² Specialist Clinical Pharmacist, Manchester Royal Infirmary, CMFT, UK
³ Consultant Rheumatologist & Honorary Senior Lecturer, Manchester Royal Infirmary, CMFT, UK
⁴ Strategic Medicines Optimisation Pharmacist, Greater Manchester Shared Services, UK
⁵ Consultant Rheumatologist & Senior Lecturer, SRFT, UK
⁶ Professor of Rheumatology, Manchester Royal Infirmary, CMFT, UK
DOCUMENT CONTROL

Revision history
The latest and master version of this document is held on the GMMMG website

<table>
<thead>
<tr>
<th>REVISION DATE</th>
<th>ACTIONED BY</th>
<th>SUMMARY OF CHANGES</th>
<th>VERSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 2016</td>
<td>Meghna Jani, Vanessa Reid &amp; Sarah Jacobs</td>
<td>Version 3 updated with up to date references and guidelines, with the same format as AS/PsA pathway, NICE guidance and biosimilars</td>
<td>3.1</td>
</tr>
<tr>
<td>Nov 2016</td>
<td>Meghna Jani</td>
<td>Abbreviated text prior to pathways, addition of TA415, modified content in pathways as per GMMMG working group discussions, updated formatting issues</td>
<td>3.2</td>
</tr>
<tr>
<td>Dec 2016</td>
<td>Sarah Jacobs</td>
<td>Checked accuracy of references, comparison to other biologics pathways, formatting</td>
<td>3.3</td>
</tr>
<tr>
<td>March 2017</td>
<td>Ben Parker</td>
<td>Additional checking and amendments</td>
<td>3.4</td>
</tr>
<tr>
<td>March 2017</td>
<td>Meghna Jani</td>
<td>Final amendments and update references. Added pre-biologic screening section</td>
<td>3.5</td>
</tr>
<tr>
<td>June 2017</td>
<td>Meghna Jani, Ben Parker, Vanessa Reid</td>
<td>Changes made post consultation comments</td>
<td>3.6</td>
</tr>
<tr>
<td>July 2017</td>
<td>Sarah Jacobs</td>
<td>Final changes post consultation – added free of charge statement, updated special situations sections. Add reference to baricitinib NICE TA466</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Approvals
This document must be approved by the following before distribution:

<table>
<thead>
<tr>
<th>NAME</th>
<th>DATE OF ISSUE</th>
<th>VERSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA working group</td>
<td>June 2017</td>
<td>4.0</td>
</tr>
<tr>
<td>HCDSG</td>
<td>26th July 2017</td>
<td>4.0</td>
</tr>
<tr>
<td>GMMMG</td>
<td>17th August 2017</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Distribution
Final version available on GMMMG website
<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Introduction</td>
<td>4</td>
</tr>
<tr>
<td>2. Aims</td>
<td>4</td>
</tr>
<tr>
<td>3. NICE guidance</td>
<td>4</td>
</tr>
<tr>
<td>4. Biosimilars</td>
<td>5</td>
</tr>
<tr>
<td>5. Individual Funding Requests</td>
<td>5</td>
</tr>
<tr>
<td>6. Research recruitment</td>
<td>6</td>
</tr>
<tr>
<td>7. Pre-biologic screening</td>
<td>6</td>
</tr>
<tr>
<td>8. Special situations</td>
<td>6</td>
</tr>
<tr>
<td>a) Peri-operative risk</td>
<td>6</td>
</tr>
<tr>
<td>b) Pregnancy and breast feeding</td>
<td>7</td>
</tr>
<tr>
<td>c) Vaccination of infants</td>
<td>8</td>
</tr>
<tr>
<td>9. Vaccinations</td>
<td>8</td>
</tr>
<tr>
<td>a) Live vaccines</td>
<td>8</td>
</tr>
<tr>
<td>b) Non-live vaccines</td>
<td>9</td>
</tr>
<tr>
<td>10. Pathway for 1st choice biologic agent in combination with methotrexate</td>
<td>10</td>
</tr>
<tr>
<td>11. Pathway for primary non-responders to biologic agent on concomitant methotrexate</td>
<td>11</td>
</tr>
<tr>
<td>12. Pathway for secondary non-responders to anti-TNF agent on concomitant methotrexate</td>
<td>12</td>
</tr>
<tr>
<td>13. Pathway for monotherapy (patients not on methotrexate)</td>
<td>13</td>
</tr>
<tr>
<td>14. Suggested checklist for patient screening on pre-admission for biologic agents</td>
<td>14</td>
</tr>
<tr>
<td>15. Specific monitoring considerations for tocilizumab and rituximab</td>
<td>15</td>
</tr>
<tr>
<td>16. Appendices</td>
<td></td>
</tr>
<tr>
<td>Appendix 1: NICE guidance</td>
<td>17</td>
</tr>
<tr>
<td>Appendix 2: Contraindications, special warnings and precautions</td>
<td>19</td>
</tr>
<tr>
<td>17. References</td>
<td>20</td>
</tr>
</tbody>
</table>
Harmonised Biologics Pathway for Rheumatoid Arthritis (RA)

1. Introduction

The pathway is to be used as a guideline for the use of biologic agents in rheumatoid arthritis (RA). It has been written using up to date published research and evidenced based medicine. This has been a clinical project implemented by MAHSC, a joint project between Rheumatology departments at Salford Royal Hospital, Central Manchester University Hospitals and the University of Manchester, extended to the GMMMG trusts.

2. Aims

The aims of the harmonised biologics pathway for RA are to:

1. Illustrate particular instances where the use of a particular biologic drug may be preferred over another, based on current safety and efficacy data.
2. Present the evidence for monotherapy (treatment without methotrexate) with rituximab and abatacept in order to enable consistent evidence based clinical practice and reduce the number of Individual Funding Requests (IFRs) across the region.
3. Advise on use of a biologic, where one treatment line is stopped within one month of initiation due to severe adverse event (e.g. injection site reaction).
4. Present the evidence and recommendations for dose reduction in patients who have responded to therapy and whose disease is stable.
5. Alert clinicians about on-going recruitment into clinical studies where appropriate.
6. Promote cost containment by using the most appropriate biologic therapy by supporting the use of cheaper therapies, biosimilar drugs, and by promoting dose reduction, where appropriate.

3. NICE guidance

The links to relevant NICE guidance are listed below (additional information in Appendix 1). Any new high cost drugs that are approved by NICE between GMMMG-RA pathway iterations will be considered for placement in this pathway. The use of any new NICE approved high cost drugs prior to inclusion in the pathway are not excluded for use. They should be used in accordance with the associated NICE TA and should not result in an increase in the number of treatment options agreed within this pathway.

The NICE recommendations also apply to biosimilar products of the technologies that have a marketing authorisation, allowing the use of the biosimilar for the same indication.

NICE (Jan 2016): Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed; TA 375

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
  - disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
  - disease has not responded to intensive therapy with a combination of conventional disease-modifying anti-rheumatic drugs (DMARDs) and
  - the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes.
- Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the above criteria are met.

NICE (Aug 2010): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor; TA195

NICE (Oct 2016): Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor; TA 415

NICE (June 2011): Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs; TA225

NICE (Feb 2012): Tocilizumab for the treatment of rheumatoid arthritis; TA247
Janus kinase (JAK) inhibitors are a new class of drug. They are orally available disease-modifying anti-rheumatic drugs with similar efficacy to biologics.

NICE (Aug 2017): Baricitinib for moderate to severe rheumatoid arthritis; TA466

4. Biosimilars

In February 2015, updated in January 2017, the British Society of Rheumatology (BSR) published guidance on the use of biosimilar infliximab in rheumatological disease:

BSR Guidance on the Use of Biosimilar medicines

GMMMG Prescribing of high cost biosimilar biological medicines, July 2016 position statement has been approved by the region’s rheumatology centres and is included in this pathway. This states:

Use of biosimilars when initiating treatment with a biologic

- The choice of biologic used should be guided in the first instance by clinical judgement (as informed by factors suggested in this pathway) based on national or local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.
- If more than one drug treatment is suitable, the least expensive option in the class of drug should be chosen (taking into account administration costs, dosage and price per dose). **You may be expected to retrospectively audit your practice, for which we recommend keeping an accurate record of the cheapest biologic for your trust (and update this on a 6-12 monthly basis).**
- When the biologic treatment has been selected, the least expensive product, either biosimilar or originator should be prescribed.
- If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if required.
- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.
- In line with MHRA guidelines: Gov.uk/drug-safety-update/biosimilar-products biologics, including biosimilars must be prescribed by brand name to support on-going pharmacovigilance of the individual products.
- Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the black triangle. Patients prescribed a biologic should be enrolled on to relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.

Changing from originator to a biosimilar

- There is accumulating evidence that patients who are in a stable clinical response or remission may be changed over to the biosimilar at the same dose and dose interval. This should only be done after discussion and agreement with individual patients with an explanation for the reason for changing.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

5. Individual Funding Requests (IFR)

- IFRs for RA will not be required for up to 4 biologics, if prescribed according to this pathway.
- All other treatment options outside of this pathway will require an IFR to be approved prior to treatment being started.
- Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the PbR excluded high cost drugs will be made by meeting the accepted criteria outlined on completion and submission of a Blueteq form.
6. Research Recruitment

All free of charge schemes and clinical trials should be approved in accordance with trust guidance and GMMMG guidance when available. Approval should be agreed at the trust’s medicines management committee. There must be clear exit criteria that does not place financial burden on commissioners and does not raise patient’s expectations of continuation of treatment.

All patients initiated on a biologic drug, including biosimilars, are encouraged to be recruited to a biologics register, where possible.

Clinical trials:

- Many sites host early and later phase clinical trials of biologic therapies, in both biologic-naïve and biologic-experienced patients.
- If eligible, patients should be considered for recruitment into a clinical trial, to facilitate both improved care and support cost containment.

BSRBR-RA:

- The BSRBR-RA is actively recruiting patients receiving
  - a biosimilar
  - certolizumab pegol
  - tocilizumab
- It is also recruiting a new contemporary control cohort of patients who were biologic naïve when they were prescribed etanercept, infliximab or adalimumab in the last 6 months.
- Visit www.rheumatology.org.uk/bsrbr or email biologics.register@manchester.ac.uk

BRAGGSS:

- All Caucasian RA patients who are about to commence treatment with a biologic will be eligible for recruitment to the BRAGGSS study.
- The aim of BRAGGSS is to investigate whether genetic/serological factors can be used to predict response to treatment with biologic drugs.
- The research nurse in your unit should be able to recruit to this study or email the study co-ordinator for BRAGGSS deborah.maskell@manchester.ac.uk

7. Pre-biologic screening

Please refer to the checklist provided at the end of the document (can be adapted locally if necessary).

- Interferon gamma (gIFN) testing is recommended in patients at risk of TB pre-biologic treatment. In patients with high index of suspicion/risk of TB consider referring to previously published algorithms for additional screening and referral for a respiratory opinion if deemed necessary: NICE (Jan 2016) Tuberculosis, NG33
- With anti-TNF therapy, risk of TB reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). There also appears to be a signal of concern from clinical trials with newer monoclonal antibodies such as certolizumab and golimumab, however data from observational studies is currently lacking.
- Screening for hepatitis B is all recommended for all patients starting a biologic, particularly rituximab: MHRA (Dec 2013) Rituximab: screen for hepatitis B virus before treatment

8. Special Situations

a) Peri-operative risk

Prevention of potential post-operative infection risk by temporarily stopping a patient’s biologic treatment should be carefully balanced against the possibility of a peri-operative flare of RA.

Should treatment be stopped prior to surgery, consider stopping the drug 3-5 times the half-life for the relevant drug. (See table 1.)

Treatment should not be recommenced post operatively until infection is excluded and the wound is healed.
**Table 1**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Half-life (days)*</th>
<th>Time to stop treatment prior to surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 days (approx 70 hours)</td>
<td>9 – 15 days</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>12-14 days</td>
<td>6 - 10 weeks</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9 days</td>
<td>4 - 7 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12-14 days</td>
<td>5 - 10 weeks</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>14 days</td>
<td>6 – 10 weeks</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Median half-life 20 days (9-36 days)</td>
<td>8 – 14 weeks</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>8 - 14 days depending on concentration (4 weeks for joint replacement)</td>
<td>4 - 10 weeks</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Median half-life 13 days (8-25 days)</td>
<td>5 – 9 weeks</td>
</tr>
</tbody>
</table>

*summary of product characteristics (SPC) May 2017

**b) Pregnancy and breast feeding**

**i) Pregnancy**

BSR issued guidance on prescribing drugs in pregnancy and breastfeeding in January 2016: [BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding](#).

There is limited data for safety of biologic drugs in pregnancy and lactation. The decision to continue biologic agents in pregnancy needs to be individualised. This needs to take into account alternative therapies, the severity of the mother’s condition prior to therapy, the risk of a disease flare by cessation of therapy, and the impact of a flare on the mother and the unborn child. This should be discussed by a multi-disciplinary team.

Patients who stop therapy during pregnancy should be re-loaded with biological therapy soon after delivery.

Consideration should be given to stopping biologic therapy in a woman who becomes pregnant as listed in table 2:

**Table 2**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Contraceptive advice – time to continue contraception after discontinuation of therapy</th>
<th>Compatible with First Trimester</th>
<th>Compatible with Second/Third Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>3 weeks</td>
<td>Yes</td>
<td>Second but not third</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5 months</td>
<td>Yes</td>
<td>Second but not third</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6 months</td>
<td>Yes</td>
<td>Stop at 16 weeks</td>
</tr>
<tr>
<td>Golimumab</td>
<td>6 months</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>5 months</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Rituximab</td>
<td>12 months</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>3 months</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Abatacept</td>
<td>14 weeks</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**ii) Breast feeding**

There is insufficient information on the excretion of biologics in breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot be excluded. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman.

The manufacturers recommend that it is not advisable to breast feed during drug treatment or for the duration specified below after treatment has stopped.

Table 3 shows the time to elapse between stopping treatment and starting breastfeeding as recommended in the SPC (June 2017)
Table 3

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time to elapse between stopping treatment and starting breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>No advice</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>5 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>6 months</td>
</tr>
<tr>
<td>Golimumab</td>
<td>6 months</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>No advice</td>
</tr>
<tr>
<td>Rituximab</td>
<td>12 months</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>No advice</td>
</tr>
<tr>
<td>Abatacept</td>
<td>14 weeks</td>
</tr>
</tbody>
</table>

c) Vaccination of Infants

If a biologic has been continued later in pregnancy, live vaccines should be avoided in the infant until they reach 6 months of age, after which time vaccination should be considered. The risk of a natural rotavirus infection is high. Although there is limited evidence of safety and efficacy in infants with immunosuppression the vaccine may be considered by the treating consultant. This does not include infants with severe combined immune deficiency. If breastfeeding, the BCG vaccination should not be given until 6 months after finishing breastfeeding. Current vaccination strategies with non-live vaccines for infants who have been exposed to biologic medicines in utero do not differ from those for unexposed infants.

9. Vaccinations

During biologic therapy, influenza vaccine patients should receive influenza vaccine annually and pneumococcal vaccine once. (Check titres every 5-10 years).

a) Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents. It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy, when necessary. There is no contra-indication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs. Table 4 shows all live vaccines available in the UK:

Table 4

<table>
<thead>
<tr>
<th>Live Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guerin Vaccine</td>
</tr>
<tr>
<td>Influenza</td>
<td>Fluenz Tetra®</td>
</tr>
<tr>
<td>Measles, Mumps and Rubella combined vaccine (MMR)</td>
<td>MMRvaxPRO®, Priorix®</td>
</tr>
<tr>
<td>Poliomyelitis (Live oral vaccine)</td>
<td>Poliomyelitis Vaccine, live (oral) GSK OPV</td>
</tr>
<tr>
<td>Rotavirus (Live oral vaccine)</td>
<td>Rotarix®</td>
</tr>
<tr>
<td>Typhoid (Live oral vaccine)</td>
<td>Vivotif®</td>
</tr>
<tr>
<td>Varicella-Zoster Vaccine</td>
<td>Varilrix®, Varivax®, Zostavax®</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Stamaril®</td>
</tr>
</tbody>
</table>

When a live vaccine is required by a patient on a biologic, the cessation of treatment may permit a necessary vaccination to be administered. Table 5 shows the time period required to elapse off each biologic therapy, prior to the administration of a live vaccination:

Table 5

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time to elapse before giving a live vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2 months</td>
</tr>
<tr>
<td>Golimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1 month</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>3 months</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6 months</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Abatacept</td>
<td>3 months</td>
</tr>
</tbody>
</table>
b) Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies. Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor. Patients treated with rituximab may receive non-live vaccinations. Vaccinations should ideally be completed at least 4 weeks prior to first administration of rituximab (due to a risk of reduced response). Vaccinations for influenza, swine flu and pneumococcal infection are still advisable for patients on rituximab.

Table 6 gives a list of non-live vaccines available in the UK.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera Vaccine (Oral preparation only)</td>
<td>Dukural®</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation.</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Avaxim®, Epaxa®, Havrix Monodose®, Vaqta Paediatric®</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Engerix®, Fendrix®, HBvaxPRO®</td>
</tr>
<tr>
<td>Hepatitis A and B combined</td>
<td>Ambirix®, Twinrix®</td>
</tr>
<tr>
<td>Influenza</td>
<td>Agrippal®, Begrivac®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, Mastaflu®, Optaflu® &amp; Viroflu®</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Pneumovax II® (Adults and Children over 5 years), Prevenar® (Primary childhood immunisation)</td>
</tr>
<tr>
<td>Poliomyelitis (Injection)</td>
<td>Inactivated Poliomyelitis Vaccine (non-proprietary) IPV</td>
</tr>
<tr>
<td>Meningococcal Group C</td>
<td>Menjugate Kit®, NeisVac-C®</td>
</tr>
<tr>
<td>Meningococcal polysaccharide A,C, W135 and Y vaccine</td>
<td>ACWY Vax®</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabipur®</td>
</tr>
<tr>
<td>Tetanus</td>
<td>*Single preparation no longer available. Combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>TicoVac®</td>
</tr>
<tr>
<td>Typhoid (Polysaccharide injection for vaccination)</td>
<td>Typhenix®, Typhim Vi®</td>
</tr>
</tbody>
</table>
10. Pathway for 1st Choice Biologic Agent in Combination with Methotrexate

Consider patient factors:
- Device
- Level of dexterity
- Frequency
- Route
- Adherence to biologic/DMARDs

Enter into BSRBR-RA (eligible if considering 1st line etanercept/adalimumab/infliximab/certolizumab/\textit{any biosimilar})
Enter into clinical trial where criteria met

Choose most appropriate agent and if no clear indication for a specific agent then use the least expensive biologic (listed in alphabetical order):
- Abatacept + MTX (TA375) or
- Adalimumab + MTX (TA375) or
- Certolizumab pegol + MTX (TA375) or
- Etanercept + MTX (TA375) or
- Golimumab + MTX (TA375) or
- Infliximab + MTX (TA375) or
- \textit{Tocilizumab} + MTX (TA375)

In the absence of any specific circumstances as below, use the least expensive biologic at the time of initiation (Please also refer to biosimilar statement)

Consider non-anti-TNF biologic (RTX/ABT/TOC) as 1st line if:
- SLE/CTD overlap
- CHF stage 3
- Felty’s syndrome
- Previously treated lymphoproliferative disorders
(ACR 2015 recommendations)

Rituximab can be used 1st line if (EULAR) and ACR recommendations (monotherapy unlicensed):
- Recent history of lymphoma
- Latent TB with contraindications to the use of chemotherapy
- Previous history of demyelinating disease
- If SLE is the predominant condition consult NICE

England advice on RTX
** CHF stage 3 is not listed as a CI on SPC

Below are specific circumstances that may suggest the use of a specific agent (in alphabetical order):

With all biologics there may be a generalised increased risk of infection. In specific circumstances such as interstitial lung disease or D) careful assessment prior to treatment, systematic subsequent monitoring (refer to previously published algorithm(s) if required) and respiratory opinion is advised regardless of chosen biologic.

#Abatacept:
- Consider if injection site reactions to anti-TNFs or (Level Ib evidence, grade of recommendation B)
- Consider if previous hospitalised infections or anti-TNFs/potential serious infection risk (Level III evidence, grade of recommendation C)
- Seropositive patients

#Adalimumab:
- Extra articular features/co-existent conditions such as:
  - Uveitis (Level I evidence, grade of recommendation C)
  - Psoriasis (TA146)
  - Crohn’s disease (TA187)
  - Ulcerative colitis (TA329)
  - Hidradenitis suppurativa (TA392)

#Certolizumab pegol:
- Women planning a pregnancy in near future (low placental transfer)

#Etanercept:
- Potential risk of TB (Level III evidence, grade of recommendation C)
- Women planning pregnancy in near future (shortest time of discontinuation prior to conception - see page 49)

- Consider if potential serious infection risk (Level III evidence, grade of recommendation C)
- Hepatitis C (Only after hepatology consultation: Level III evidence, grade of recommendation C)

#Golimumab:
- Consider if patient over 100kg (Patient access to double dose)
- Needle phobia/compliance issues/patient convenience
- Ulcerative colitis (TA329)

#Infliximab:
- Body weight >60kg (potential cost saving)
- Compliance issues/ needle phobia
- Severely impaired manual dexterity
- Crohn’s disease (TA187) and Ulcerative colitis (TA329)

- Psoriasis (TA134)
- Rheumatoid vasculitis (Level IV evidence, grade of recommendation D)

#Tocilizumab:
- Features of IL-6 mediated disease (high ESR/CRP, anemia of chronic disease, high ferritin)
- AA Amyloidosis (Level IV evidence, grade of recommendation D)

*Intravenous infusion **monthly dosing, #SC and IV versions available.
11. Pathway for Primary Non-Responders to Biologic Agent in Combination with Methotrexate

Choose most appropriate agent and if no clear indication for a specific agent then use the least expensive biologic (listed in alphabetical order):
- Abatacept + MTX (TA375) or
- Adalimumab + MTX (TA375) or
- Certolizumab pegol + MTX (TA375) or
- Etanercept + MTX (TA375) or
- Golimumab + MTX (TA375) or
- Infliximab + MTX (TA375) or
- Tocilizumab + MTX (TA375)

If yes: Consider an alternative biologic or rituximab (TA195). (Patients can be switched to another anti-TNF agent if they experience an adverse event within 6 months)

Enter into BSRBR-RA (eligible if considering 2nd line if considering certolizumab/ Tocilizumab/ any biosimilar Consider clinical trial where eligible.

Enter into BSRBR-RA (eligible if considering 2nd line if considering certolizumab/ Tocilizumab/ any biosimilar Consider clinical trial where eligible.

Has the biologic agent been withdrawn because of an adverse event within 6 months of treatment?

Primary non-response to 1st biologic (on MTX)
- Non response to certolizumab after 3 months
- Non response to any other biologic agent after 6 months

Seropositive **

Does the patient have a C3 to rituximab?

No

Rituximab + MTX (TA195)

Continue rituximab + MTX (TA195) only if adequate response (improvement of DAS28 of 1.2 points or more). Should be given no more frequently than 6 months.

Yes

Has the patient:
- Developed a C3 to rituximab?
- Withdrawn due to an adverse event?
- Non-response to rituximab?

Abatacept + MTX (TA195)
- Adalimumab + MTX (TA195)
- Certolizumab Pegol + MTX (TA415)
- Etanercept + MTX (TA195)
- Infliximab + MTX (TA195)
- Tocilizumab + MTX (TA247)

Primary non-response: Lack of improvement of clinical signs and symptoms to induction therapy (i.e. when the patient has not ever responded to the drug)

**New evidence suggests seropositive patients (anti CCP or RF) are more likely to have a greater response with abatacept than patients who are seronegative. May be considered as an additional option instead of rituximab 37, 44.

*SC & IV versions available (IV can be used if clinician feels this is most appropriate) after evaluation of patient factors listed on page 10
12. Pathway for Secondary Non- Responders to Biologic Agent in Combination with Methotrexate

Secondary failure of 1st anti-TNF inhibitor on MTX: Defined as initial response to anti-TNF followed by loss of efficacy after 3-6 months

- Consider measurement of anti-drug antibodies (ADA) and trough drug levels (as part of a clinical study if available locally) 31-42

- ADA-ve and low drug levels
  - Assess adherence to biologic 31,39
  - Consider BMI: Is the dose weight adjusted? 31,39

- ADA-ve and high drug levels
  - Switch to a non anti-TNF biologic drug (rituximab/*tocilizumab/*abatacept) 31,39

- ADA+ve and low drug levels
  - Has etanercept been used 1st line?
    - No
      - Switch to etanercept (less immunogenic)

- Seropositive**
  - Does the patient have a CI to Rituximab?
    - No
      - Rituximab + MTX (TA195)
  - Yes
    - Anti-TNF agent with different mechanism of action (i.e. monoclonal antibodies) + MTX (TA195) or Tocilizumab + MTX (TA247) or Abatacept + MTX (TA195) or Certolizumab + MTX (TA415)

Continue rituximab + MTX (TA195) only if adequate response (improvement of DAS28 of 1.2 points or more) should be given no more frequently then every 6 months.

- Developed a CI to rituximab?
  - Yes
    - Tocilizumab + MTX (TA247)
    - Abatacept + MTX (TA195)
    - Anti-TNF + MTX (TA195)
  - No
    - Yes

Secondary non-response to a non-anti-TNF biologic and etanercept has limited data to support best practice around subsequent biologic use. Therefore treatment decisions in such cases should be as per NICE recommendations

**New evidence suggests seropositive patients (anti CCP or RF) are more likely to have a greater response with abatacept than patients who are seronegative. May be considered as an additional option instead of rituximab37,42.

*S/C & IV versions available (IV can be used if clinician feels this is most appropriate) after evaluation of patient factors listed on page 10

Monoclonal antibodies include adalimumab, certolizumab, golimumab and infliximab

ADA: Anti-drug antibodies (check against monoclonal antibodies only, not detected against etanercept)42.

Drug trough level: Blood sample collected before next drug administration
13. Pathway for Monotherapy (Patients not on Methotrexate)

If yes: Consider an alternative biologic or rituximab (TA195). (Patients can be switched to another anti-TNF agent if they experience an adverse event within 6 months.
Enter into clinical trial and BSRBR-RA where criteria met
Consider patient factors

Choose most appropriate agent and if no clear indication for a specific agent then use the least expensive biologic (listed in alphabetical order):
- *Abatacept not recommended by NICE 18,19 or Adalimumab (TA375) or Certolizumab pegol (TA415) or Etanercept (TA375) or *Tocilizumab (TA375)

Has the biologic agent been withdrawn because of an adverse event within 6 months of treatment?

No

Primary non-response to 1st biologic
- Non response to certolizumab after 3 months
- Non response to any other biologic agent after 6 months

Consider non-anti-TNF biologic (RTX/ABT/TOC) as 1st line if:
- SLE/CTD overlap *
- CHF stage 3**
- Felty's syndrome 19
- Previously treated lymphoproliferative disorders (ACR 2015 recommendations) 20

Rituximab can be used 1st line if [EULAR 18 and ACR 219 recommendations]:
- Recent history of lymphoma 18, 20
- Latent TB with contraindications to the use of chemotherapy 18
- Previous history of demyelinating disease 18
*If SLE is the predominant condition consult NHS England advice on RTX
**CHF stage 3 is not listed as a CI on SPC

Seropositive

Does the patient have a CI to rituximab and leflunomide?

No

Rituximab + leflunomide (BSR guidelines 2011)†
Rituximab monotherapy if not on MTX or leflunomide. RTX monotherapy should only be considered in exceptional circumstances (e.g. Cl to anti-TNF and Tocilizumab)
Continue rituximab + leflunomide 2  or rituximab monotherapy only if adequate response (improvement of DAS28 of 1.2 points or more). Should be given no more frequently than 6 months.

Yes

Has the patient had:
- A Cl to rituximab or leflunomide?
- Rituximab or leflunomide been withdrawn due to an adverse event/non-response?

Yes

*Abatacept 18,19 (see above note in red) †
*Tocilizumab (TA375) †

Seronegative

Consider Alternative Biologic:
Adalimumab (TA195) or etanercept (TA195) or certolizumab (TA375) or *Tocilizumab (TA247) †
*Abatacept 18,19 †
Abatacept monotherapy should only be considered in exceptional circumstances (e.g. Cl to anti-TNF and Tocilizumab)

Adequate response to treatment at 6 months (DAS28 score improved by ≥ 1.2)?

Yes

Continue with 6-12 monthly monitoring. Withdraw if adequate response not maintained.

No

If primary non-response switch to biologic with different mechanism of action (e.g. Tocilizumab/RTX/ABT monoclonal antibody if not tried already).

If secondary non-response to adalimumab/certolizumab consider changing to less immunogenic biologic agent (e.g. etanercept if not tried already) see algorithm above 18,20

*S/C and IV versions available (IV can be used if clinician feels this is the most appropriate) after evaluation of patient factors listed on page 6. †Use in monotherapy is off license
14 Suggested checklist for patient screening on pre-admission for biologic agents

Name:…………………………………………………… Number:…………………………………………………. Consultant:…………………

<table>
<thead>
<tr>
<th>Screening Investigations Requested in Clinic</th>
<th>Y/N</th>
<th>Initial</th>
<th>Results/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC/U&amp; ESLFT/ESR/CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Factor (if negative check anti-CCP) Don’t repeat if previously positive result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA (if positive also order ENA/dsDNA/C3/C4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV, HBV (surface antigen, core antibody)*; HCV (antibody test) If positive result please refer to Hepatology/GUM * Reactivation has been reported in HBsAg-ve as well as HBsAg +ve patients stressing the importance of measuring not only HBsAg but also antibodies against Hbc antigen to identify positive carrier status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella Zoster IgG (if negative inform GP and patient)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB screening (g-IFN testing) If positive refer to respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-Ray (within the last 6 months) (± pulmonary function tests/HRCT thorax)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR checked by/date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Immunoglobulins (document low IgG: monitor if low especially in older patients) (+/- B Cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipids (if abnormal treat according to local guidelines)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening Questions Asked in Clinic</th>
<th>Y/N</th>
<th>Initial</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous TB/TB contact (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent travel abroad (i.e. TB high risk countries)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Which Country/Dates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of heart failure (NYHA class III or IV) (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of recurrent infection (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of interstitial lung disease (details such as extent of ILD**1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cancer (Type/Date when occurred/Date of all clear)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of last mammogram (50yr +) (Encourage patient to visit GP if &gt;3 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of last smear (25yr +) (Encourage patient to visit GP if &gt;3 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of infusion reaction to any agent (To what/type of reaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy (details)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverticulitis (caution advised due to perforation risk, especially if also on NSAIDs or oral steroids)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education and Funding</th>
<th>Initial</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request for funding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy/breastfeeding advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual influenza vaccination advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination advice given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient counselled and educated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient education pack given</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient consent to be approached for research</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Completing Clinician Signature…………………………………………………… Date…………………………

Nurse Practitioner Signature…………………………………………………… Date…………………………
Specific monitoring considerations for tocilizumab and rituximab

**Tocilizumab Recommendations**

| FBC (monitoring of absolute neutrophil count [ANC]) | • Check ANC the week before next infusion or 4 weekly if on subcutaneous injection for the first 6 months  
• If significant neutropenia does not occur during first 6 months, reduce to every 12 weeks thereafter |
| LFTs (in monotherapy and in combination with DMARDs) | • LFTs should be monitored 4-weekly for first 6 months  
• Tocilizumab monotherapy: if no LFT abnormalities are detected at the end of 6 months, less frequent monitoring (every 2-3 months) may be acceptable.  
• Tocilizumab and concomitant DMARDs (including methotrexate): as the incidence of LFT abnormalities is considerably higher, recommend that 4-week tests be continued for the duration of tocilizumab therapy. Tests should be carried out in the week leading up to the next infusion and 4 weekly if on the subcutaneous injection. |
| Lipid profile | • All patients should have a repeat fasting lipid profile in 3 months after starting tocilizumab and treatment instituted/ altered if appropriate  
• Further monitoring should be guided by local practice and existence of other risk factors.  
(Patients may have lipids monitored every 4-8 weeks after initiation as per SPC in patients at risk or as per clinical judgement. In most published RCTs to date, lipids stabilized after initial few months of treatment) |

**Rituximab recommendations**

| Serum immunoglobulins | • IgG should be monitored in patients treated with rituximab, particularly in those who demonstrate low baseline levels, with close monitoring particularly in higher risk patient groups such as the older patient (associated with increased infection risk).  
• More frequent decreases in IgM, in contrast, have not been associated with increased rates of infections |

Managing side effects of tocilizumab:

**Low absolute neutrophil count (ANC)\(^{13}\)**

Initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/l

<table>
<thead>
<tr>
<th>Laboratory Value (cells x 10^9/l)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt; 1</td>
<td>Maintain dose.</td>
</tr>
</tbody>
</table>
| ANC 0.5 to 1 | Interrupt tocilizumab dosing  
• IV: When ANC > 1 resume at 4mg/kg and increase to 8mg/kg as clinically appropriate  
• S/C: When ANC increases > 1 resume tocilizumab dosing every other week and increase to every week injection, as clinically appropriate. |
| ANC < 0.5 | Discontinue tocilizumab |

**Low platelet count**

<table>
<thead>
<tr>
<th>Laboratory Value (cells x 10^7/μl)</th>
<th>Action</th>
</tr>
</thead>
</table>
| 50 to 100 | Interrupt tocilizumab dosing  
• IV: When platelets > 100 resume at 4mg/kg and increase to 8mg/kg as clinically appropriate  
• S/C: When platelet count >100 resume tocilizumab dosing every other week and increase to every week injection as clinically appropriate |
| < 50 | Discontinue tocilizumab |
**Abnormal LFTs**

<table>
<thead>
<tr>
<th>Laboratory Value</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 to 3 x Upper Limit of Normal (ULN)</td>
<td>Dose modify concomitant DMARDs if appropriate</td>
</tr>
<tr>
<td></td>
<td>• IV: For persistent increases in this range reduce dose to 4mg/kg or interrupt until ALT/AST have normalised</td>
</tr>
<tr>
<td></td>
<td>• S/C: Reduce tocilizumab dose frequency to every other week injection or interrupt tocilizumab until ALT/AST have normalised. Restart with weekly or every other week injection, as clinically appropriate.</td>
</tr>
<tr>
<td>&gt; 3 to 5 x ULN</td>
<td>Interrupt tocilizumab dosing until &lt; 3 x ULN and follow recommendations above for &gt; 1 to 3 x ULN. For persistent increases &gt; 3 x ULN (confirmed by repeat testing), discontinue tocilizumab</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>Discontinue tocilizumab</td>
</tr>
</tbody>
</table>
16. Appendices

Appendix 1: NICE guidance

NICE (Jan 2016): Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed; TA375

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
  - disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
  - disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and
  - the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes.

- Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in section 1.1 are met.

- Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy.

- Start treatment with the least expensive drug (taking into account administration costs, dose needed and product price per dose). This may need to be varied for some people because of differences in the mode of administration and treatment schedules.

NICE (Aug 2010): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor; TA195

- Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other DMARDs including at least one TNF inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

- Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreatment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.

- Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.

- Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event.

- Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained.

- When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

- A team experienced in the diagnosis and treatment of rheumatoid arthritis and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.

NICE (Oct 2016): Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor; TA 415

Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 TNF inhibitor, only if:
- disease activity is severe
- rituximab is contraindicated or not tolerated and
- the company provides certolizumab pegol with the agreed patient access scheme.

Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if:
- disease activity is severe and
- rituximab therapy cannot be given because methotrexate is contraindicated or not tolerated and
- the company provides certolizumab pegol with the agreed patient access scheme.

**NICE (June 2011): Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs; TA225**

The first part of the recommendation has been replaced by the recommendations in the NICE TA 375 (above). Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if:
- it is used as described for other TNF inhibitor treatments in ‘Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor’ (NICE technology appraisal guidance 195), and
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
- When using the disease activity score (DAS28), healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.

**NICE (2012): Tocilizumab for the treatment of rheumatoid arthritis; TA247**

The first part of the recommendation has been replaced by the recommendations in the NICE TA 375 (above). Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for other anti-TNFs in (NICE technology appraisal guidance 195), specifically the recommendations on disease activity or
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab
- the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

**NICE (Aug 2017): Baricitinib for moderate to severe rheumatoid arthritis; TA466**

Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs), only if:
- disease is severe (a disease activity score [DAS28] of more than 5.1) and
- the company provides baricitinib with the discount agreed in the patient access scheme

Baricitinib, with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to or who cannot have other DMARDs, including at least 1 biological DMARD only if:
- disease is severe (a DAS28 of more than 5.1) and
- the patient cannot have rituximab
- the company provides baricitinib with the discount agreed in the patient access scheme

Baricitinib can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance, when the criteria in sections 1.1 and 1.2 are met.

Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.

**NHS England guidance (Last accessed 9/10/16)**
Appendix 2: Contraindications, special warnings and precautions

a) Contraindications to anti-TNF’s (certolizumab pegol, infliximab, golimumab, adalimumab)
   - Moderate to severe heart failure (NYHA class III/IV heart)
   - Active tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections
   - History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients

   Special warnings and precautions for use with infliximab
   Medicines.org.uk: Infliximab special warnings and precautions

   Special warnings and precautions for use with golimumab
   Medicines.org.uk: Golimumab special warnings and precautions

   Special warnings and precautions for use with adalimumab
   Medicines.org.uk: Adalimumab special warnings and precautions

   Special warnings and precautions for use with certolizumab pegol
   Medicines.org.uk: Certolizumab pegol special warnings and precautions

b) Contraindications to etanercept
   - Hypersensitivity to the active substance or to any of the excipients
   - Sepsis or risk of sepsis
   - Treatment with etanercept should not be initiated in patients with active infections including chronic or localised infections

   Special warnings and precautions for use with etanercept
   Medicines.org.uk: Etanercept special warnings and precautions

c) Contraindications to abatacept
   - Hypersensitivity to the active substance or to any of the excipients
   - Severe and uncontrolled infections such as sepsis and opportunistic infections

   Special warnings and precautions for use with abatacept
   Medicines.org.uk: Abatacept special warnings and precautions

d) Contraindications to rituximab
   - Hypersensitivity to the active substance or to any of the excipients
   - Active, severe infections
   - Patients in a severely immunocompromised state
   - Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease

   Special warnings and precautions for use with rituximab
   Medicines.org.uk: Rituximab special warnings and precautions

e) Contraindications to tocilizumab
   - Hypersensitivity to the active substance or to any of the excipients
   - Active, severe infections

   Special warnings and precautions for use with tocilizumab
   Medicines.org.uk: Tocilizumab special warnings and precautions

f) Contraindications to baricitinib
   - Hypersensitivity to the active substance or to any of the excipients
   - Pregnancy

   Special warnings and precautions for use with baricitinib
   Medicines.org.uk: Baricitinib special warnings and precautions
References


