North Central London

Rheumatoid Arthritis Advanced Therapies Prescribing Pathway

Adjustment for COVID-19

Document Revision History		
Date	**Version**	**Comment/Changes**
04.07.2019	0.1	First draft
08.08.2019	0.2	Comments from stakeholder meeting 31.07.2019. Remove dose withdrawal and tapering section. Add information regarding tocilizumab and using other DMARDs when methotrexate contraindicated.
20.08.2019	0.3	Amendments to wording i.e. adequate response vs moderate response. Tocilizumab wording. Add references.
15.10.2019	0.4	Pathway updated for comments from stakeholders
15.11.2019	0.5	Updates added following JFC evidence review for rituximab first-, third-, fourth- and fifth line and second-line anti-TNF use in patients who are eligible for rituximab
07.01.2020	0.6	Seronegative definition added. Upadacitinib added alongside existing JAK inhibitors in preparation for expected NICE TA publication on 18th March 2020.
28.01.2020	0.7	Prescribing algorithm updated.
07.02.2020	0.8	Upadacitinib removed following review of proposed place in therapy. Prescribing in pregnancy clarified. Section on progressing through the pathway added.
14.05.2020	1.0	COVID-19 Adjustment: removal of 5th line. Updated references, revision history, reformatted to agreed template.
17.12.2020	1.1	Update following JFC review of rituximab use during COVID-19 and COVID-19 vaccinations.

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Scope

This document outlines the treatment pathway for adult patients with highly active rheumatoid arthritis, defined as a DAS28 score > 5.1, requiring advanced therapies: biologic DMARDs (bDMARDS) and targeted synthetic DMARDS (tsDMARDS). The use of conventional DMARDS (cDMARDS) is outside the scope of this pathway except where stated.

The Technology Appraisals (TAs) published by the National Institute for Health and Care Excellence (NICE) shown in Table 1 have been incorporated into this pathway.

Table 1: NICE Technology Appraisals for Rheumatoid Arthritis

NICE Technology Appraisal Number	Title
TA485	Sarilumab for moderate to severe rheumatoid arthritis
TA480	Tofacitinib for moderate to severe rheumatoid arthritis
TA466	Baricitinib for moderate to severe rheumatoid arthritis
TA247	Tocilizumab for the treatment of rheumatoid arthritis
TA195	Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
TA225	Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs
TA415	Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (TA415)
TA375	Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

Principles

This document is based on current NICE TAs available for the management of rheumatoid arthritis, as well as local agreements which are based on clinical evidence collated by the NCL Joint Formulary Committee (JFC).

The pathway is subject to change as new evidence, NICE TAs or local agreements are released or updated that will impact on the information outlined in this document. This includes changes in drug costs that may impact on cost-effectiveness and drug choice in the treatment pathway.

Only four lines of therapy will be commissioned by CCGs under this pathway, irrespective of the modes of action for drugs previously used. 5th line treatment and beyond is not routinely commissioned and funding for such treatment will require the submission of an Individual Funding Request where clinical exceptionality can be demonstrated.

It is expected that where possible, drugs approved for use through a NICE TA are selected in preference to non-NICE approved options. It is also expected that drugs presenting best value are selected where clinically appropriate. For further prescribing information including contraindications and cautions, please refer to the relevant drug monograph in the latest version of the British National Formulary or the respective drug's Summary of Product Characteristics.

Definitions and Lines of Therapy

The DAS28 scoring system below is used to stratify disease severity in rheumatoid arthritis.[1] The response to therapy, described by a reduction in DAS28 as defined by the European League Against Rheumatism (EULAR) is used to assess the effectiveness of treatment.

Table 2: EULAR criteria for DAS28 scores in rheumatoid arthritis[2]

Current DAS28 score	DAS28 Improvement		
	>1.2	>0.6 and ≤1.2	≤0.6
≤ 3.2	Good	Moderate	No response
>3.2 and ≤ 5.1	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

Treatment response will determine whether a drug is suitable for continued use, as is stipulated by NICE in the respective TAs.

The following definitions and timelines have been agreed to describe treatment failure (non-response or loss of response) and adverse drug reactions or intolerance.

Primary Failure
Patient does not demonstrate a moderate response to therapy in DAS28 (as defined by EULAR in Table 2) following 6 months of treatment.

An adverse drug reaction to a medicine within 6 months will not count as a line of therapy.

Secondary Failure
Patient initially achieves a moderate response to therapy in DAS28 (as defined by EULAR in Table 2) at 6 months post-initiation, which is subsequently not sustained, resulting in failure to maintain a moderate reduction in DAS28.

An adverse drug reaction to a medicine after 6 months will count as a line of therapy.

Seronegative rheumatoid arthritis
A confirmed diagnosis of rheumatoid arthritis without the presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Progressing through the pathway

The pathway is colour-coded to support the identification and thus use of the most cost-effective agents available. The expectation is that drug acquisition costs are factored into the decision-making process when selecting the most clinically appropriate drug at each line. It is anticipated that as patients move down the pathway, more expensive drugs with differing mechanisms of action will need to be selected. The rationale for using more costly agents early in the pathway will be based on clear, objective clinical situations (e.g. absolute or relative contraindications to lower-cost agents).

Biologic choice in patients unable to take methotrexate (oral and subcutaneous)

Many biologic medicines used in the management of rheumatoid arthritis are licensed for use concurrently with methotrexate. It is the preferred option to use biologics in combination with methotrexate. For drugs that are off-label when used as monotherapy, these have been reviewed and approved for use by the NCL JFC. Monotherapy (off-label) has been approved for rituximab and abatacept.

In cases where patients are unable to have methotrexate, tocilizumab monotherapy is well supported, given the availability of robust evidence (ADACTA study[3]) supporting its use as monotherapy.

In circumstances where patients are intolerant or contraindicated to methotrexate, other conventional DMARDs may be used in combination with biologics. It is the responsibility of the prescriber to identify whether these combinations may be considered ‘off-label’ and inform patients accordingly. It is expected that patient consent is obtained and clearly documented where a medicine is being used off-label.

Rituximab first-line with or without methotrexate

The first-line use of rituximab is off-label and does not hold a NICE approval. While it is licensed to be used with methotrexate, its use as monotherapy (i.e. without methotrexate) has been approved locally. It is expected that patient consent is obtained and clearly documented where any medicine is being used off-label.
First-line use of rituximab with or without methotrexate is approved in patients with:

- History of a demyelinating disease
- Interstitial lung disease (ILD)
- Recent history of malignancy
- Current diagnosis of malignancy
- History of lymphoma or other B cell lymphoproliferative disease
- Latent tuberculosis with a contraindication to the use of chemoprophylaxis

Any use outside of these circumstances is not routinely funded.

Rituximab use during COVID-19 and COVID-19 vaccinations

NCL JFC has supported a request to pause or delay rituximab as 2nd line treatment for severe rheumatoid arthritis (RA) during the COVID-19 pandemic until July 2021.

This decision follows a review of abstract/poster data which identified rituximab as an independent risk factor for adverse COVID-19 outcomes. Furthermore, there is a theoretical basis (no evidence) for rituximab reducing the effectiveness of the COVID-19 vaccination. On balance, the Committee agreed the pandemic was effectively a 'caution for use' for rituximab and consequentially it was appropriate for patients to be offered other treatment options at 2nd line as per pathway in Appendix 1. If a patient chooses to pause/delay rituximab, they should remain on their new treatment until failure. It is essential that biosimilar rituximab is not lost from the treatment pathway, therefore patients who delay rituximab use must be offered it as their 3rd line agent (unless contraindicated).

Biologic choice in pregnancy and breastfeeding

Certolizumab pegol is the drug of choice in women who are confirmed pregnant as it is compatible with all three trimesters of pregnancy.[4,5] If patients are required to be switched to certolizumab pegol due to confirmation of pregnancy, whether planned or unplanned, this will not count as a line of therapy if this drug is used for a finite duration with a planned exit strategy from its use. The drug should be reviewed to stop post parturition, reverting to the most clinical- and cost-effective agent as soon as is practicable.

For certolizumab pegol prescribed pre-conception for patients planning for pregnancy, this use will count as a line of therapy on the pathway.

For further information on the use of cDMARDs or bDMARDs in pregnancy or breast feeding, please refer to the following guidance:[4]
BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids (accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535)

Blueteq

With a view to support data-driven care, commissioners will be extracting outcomes data from Blueteq. Blueteq must therefore be used for the management of all funding requests. This includes recording treatment switches and cessation as a result of clinical review and/or remission, drug switching for patients who are confirmed or planning for pregnancy, and formulation switching during COVID-19, e.g. between intravenous and subcutaneous therapy.

Trusts are required to obtain CCG funding for the use of bDMARDs and tsDMARDs in the management of rheumatoid arthritis via Blueteq prior to starting therapy and for continuation of therapy as described on the Blueteq forms.

References

1. European League Against Rheumatism; EULAR; 2020; Online; available from: https://www.eular.org [Accessed 26 May 2020]
2. Van Riel PLM; DAS28; 2020; Online; available from: https://www.das-score.nl/das28/en/ [Accessed 26 May 2020]
3. Gabay C, Emery P, van Vollenhoven R et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013; 381 (9877): 1541-1550.
4. Flint J, Panchal S, Hurrell A et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology 2016; Volume 55 (9): 1693–1697.
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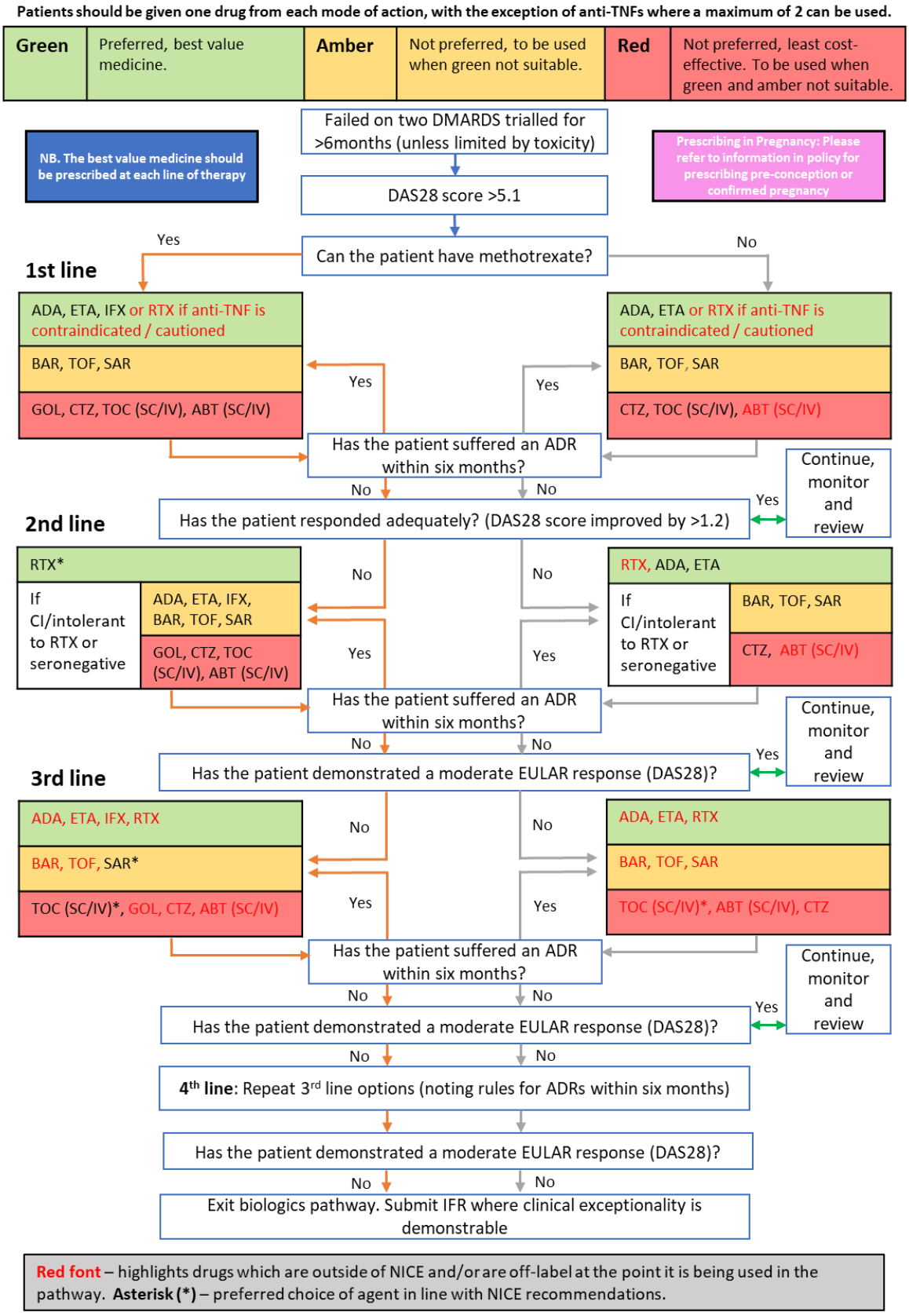
5. Summary of Product Characteristics, Cimzia 200mg solution for injection in pre-filled syringe. Last updated 26 July 2019. Available from:
   https://www.medicines.org.uk/emc/product/4450/smpc#PREGNANCY

Appendix 1. Biologic Treatment Pathway



Appendix 2. Glossary

Abbreviation	Full Term (drug class)
ABT	Abatacept (CD80/CD86 inhibitor)
ADA	Adalimumab (anti-TNF)
ADR	Adverse drug reaction
BAR	Baricitinib (JAK inhibitor)
CI	Contraindicated
CTZ	Certolizumab (anti-TNF)
DMARD	Disease modifying anti-rheumatic drug
bDMARD	Biological disease modifying anti-rheumatic drug
cDMARD	Conventional disease Modifying anti-rheumatic drug
tsDMARD	Targeted synthetic disease Modifying anti-rheumatic drug
ETA	Etanercept (anti-TNF)
GOL	Golimumab (anti-TNF)
IFX	Infliximab (anti-TNF)
MTX	Methotrexate (conventional DMARD)
RTX	Rituximab (CD20 inhibitor)
SAR	Sarilumab (IL-6 inhibitor)
TOC	Tocilizumab (IL-6 inhibitor)
TOF	Tofacitinib (JAK inhibitor)