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High-Cost Drugs Treatment Pathway for Rheumatoid Arthritis

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Document Version History		
Date	**Version**	**Comment/Changes**
This pathway was designed by the NEL Rheumatoid Arthritis working group. The pathway was pre-dated by the North East London Rheumatoid Arthritis Advanced Therapies Prescribing Pathway		
Nov 23	2	Primary failure – updated

		Requirement for an adverse reaction to occur before 6 months removed – page 6 Dose escalation for adalimumab and infliximab added – page 7 Return to previous therapy added – page 7 Patients transferring from out of area or overseas continuing on therapy added – page 8 Certolizumab for patients with moderate disease pre-conception or during pregnancy added – page 9 Safety concerns re: JAK inhibitors removed
Jan 25	2.1	Update to link in Treatment choice in pregnancy and breastfeeding section

Contents

Scope

This document outlines the treatment pathway for adult rheumatoid arthritis patients with moderate (DAS28 score ≥ 3.2 and ≤ 5.1) or severe (DAS28 score > 5.1) disease activity, 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.

NICE Guidance and Technology Appraisals

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 and supplemented by a number of locally agreed treatment options.

Table 1: NICE Technology Appraisals for Rheumatoid Arthritis

NICE TA reference	Title
TA715	Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed – (abatacept not recommended)
TA676	Filgotinib for treating moderate to severe rheumatoid arthritis
TA665	Upadacitinib for treating severe rheumatoid arthritis
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
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
TA744	Upadacitinib for treating moderate rheumatoid arthritis

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 NEL RA working group. This prescribing pathway has taken into consideration the Regional Medicines Optimisation Committee (RMOC) Advisory statement on the sequential use of biologic medicines (updated 07 May 2020) to formulate a position which meets the need of patients in the region[8].

Extensions from NICE recommendations, in the form of local agreements, aim to address an unmet clinical need for an established cohort of patients with highly active RA who are at risk of adverse outcomes due to limitations to treatment options under NICE TAs. The use of medicines outside of NICE TAs will be monitored on a regular basis through Blueteq, where utilised, or clinical audit where Blueteq is not used.

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.

For moderate disease activity (DAS28 score between 3.2 and 5.1), two mechanisms of action will be commissioned by the ICB under this pathway. Further treatment beyond this is not routinely commissioned and patients will need to exit the pathway and return to standard care.

Table 2: Mechanisms of action for moderate RA

Mechanism of action	
Anti-TNF	**JAK Inhibitors**
Adalimumab	Filgotinib
Etanercept	Upadacitinib
Infliximab	

For severe disease activity (DAS28 score over 5.1), five mechanisms of action will be commissioned by the ICB under this pathway. Further treatment beyond this is not routinely commissioned and patients will need to exit the pathway and return to standard care.

Table 3: Mechanisms of action for severe RA

Mechanism of action				
Anti-TNF	**JAK Inhibitors**	**IL-6 Inhibitor**	**CD20 Inhibitor**	**CD80/CD86 Inhibitor**
Adalimumab	Filgotinib	Sarilumab	Rituximab	Abatacept
Etanercept	Baricitinib	Tocilizumab		
Infliximab	Tofacitinib			
Golimumab	Upadacitinib			
Certolizumab				

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

Current DAS28 score	DAS28 Improvement		
	>1.2	>0.6 to ≤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 stipulated by the relevant NICE TA.

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. If a patient does not show a response within the response assessment period, the patient may start on a different biologic within the same mechanism of action without it being an additional 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.

Adverse reactions

An adverse reaction to a drug will not 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 may 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).

Treatment choice

This pathway will give patients the opportunity to access from a choice of five advanced therapies from two distinct drug classes for moderate RA and thirteen advanced therapies from five distinct drug classes for severe RA. It is the clinician's responsibility to ensure patients are well-informed of the available treatment options and receive the most clinically cost-effective (i.e. best value) and appropriate drug at each line of therapy. There may be instances where multiple drugs are chosen from one mechanism of action as this is more appropriate for the patient based on their clinical presentation (e.g. pregnancy status, comorbidities, treatment history or preference for administration route/frequency). A maximum of 5 mechanisms of action would still apply for these patients.

Return to previous treatment

Patients may exhaust the 5 available lines of therapy and a return to a previous treatment which they previously had an adequate response to may be appropriate (e.g. developed a contraindication to therapy, perceived intolerance/hypersensitivity to a previous treatment, dose escalation of previous treatment was not available etc). Patients who have exhausted the 5 mechanisms of action, but who had a response to a previous treatment will be able to return to that drug provided they achieved an adequate response previously. Returning to a previous treatment is commissioned for one drug and must be documented on the patients record and through the appropriate Blueteq form. If this treatment then fails the patient will need to exit the treatment pathway and return to standard care.

Dose escalation

As per NICE TAs 195, 375 and 715 and the product SPC patients being treated with adalimumab as monotherapy who lose response to treatment may benefit from an increase in dose to 40mg every week. Patients taking infliximab IV who have an inadequate response or who lose response may benefit from a step-wise dose escalation by 1.5mg/kg to a maximum dose of 7.5mg/kg every 8 weeks or administration of 3mg/kg every 4 weeks. Taking an anti-TNF level is recommended before starting dose escalation.

Table 5 – Dose escalation

Standard dose	Dose Escalation	Licensed Use	Notes
Adalimumab 40mg fortnightly	Adalimumab 40mg weekly for 12 weeks and review.	Yes	Only in patients not receiving methotrexate. If adequate response is achieved with 40mg every week the dosage may subsequently be reduced to

Standard dose	Dose Escalation	Licensed Use	Notes
			40mg every other week, if considered clinically appropriate.
Infliximab IV 3mg/kg every 8 weeks	Increase by 1.5mg/kg to maximum dose of 7.5mg/kg every 8 weeks OR 3mg/kg every 4 weeks	Yes	

Patients transferred from out of area or from overseas

For patients who have already commenced on their treatment for rheumatoid arthritis:

- If the current treatment is covered by a NICE TA, then the patient can continue their treatment as per the TA.
- If the treatment is not covered by a NICE TA, or this pathway, then an application to IFR must be submitted to continue the funding for therapy.

It is the responsibility of the specialist Rheumatologist to ensure the patient's GP is informed that the patient is receiving treatment with a biologic. It will then be the responsibility of the GP to update a person's medical record with this biologic.

Disease Progression

Where patient progress from moderate to severe disease whilst on therapy it is expected that drugs already used would not be requested again. However, as there are more drugs available in the severe pathway patients will be able to access all 5 mechanisms of action regardless of how many lines of therapy already accessed in the moderate pathway.

Choice of advanced therapies in patients unable to take methotrexate (oral and subcutaneous)

Many advanced therapies used in the management of rheumatoid arthritis are licensed for use concurrently with methotrexate. It is the preferred option to use these drugs in combination with methotrexate. For drugs that are off-label when used as monotherapy, these have been reviewed and approved for use by the respective Trust Drugs and Therapeutics Committees (DTCs) or equivalent within NEL. Monotherapy (off-label) has been approved for rituximab and abatacept when used for treating severe RA.

In circumstances where patients are intolerant or contraindicated to methotrexate, other cDMARDs may be used in combination with advanced therapies. 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.

Treatment 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 [3,4,5]. 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 clinically and cost-effective agent as soon as is practicable. It should be noted that certolizumab pegol has a license for use in patients with moderate disease but the manufacturer did not make a submission to have it included in TA715. Therefore, certolizumab will only be commissioned in patients with moderate disease who are planning conception or who are already pregnant until they have given birth, when they should then return to their previous therapy.

For further information on the use of cDMARDs or bDMARDs in pregnancy or breast feeding, please refer to the following guidance [3]:

- The British Society for Rheumatology (BSR) guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids (accessed via: https://academic.oup.com/rheumatology/article/62/4/e48/6783012)

Rituximab first-line with or without methotrexate (DAS28 score > 5.1 only)

For severe disease activity, 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
- RA/CTD overlap where patients have both a positive antibody test (e.g. against Ro or dsDNA) and presenting features of CTD (e.g. mild skin rash)[6,7]

Any use outside of these circumstances is not routinely commissioned.

Blueteq

With a view to support data-driven care, commissioners will be extracting outcome 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 and drug switching for patients who are confirmed or planning for pregnancy. Where Blueteq is not in use by the Trust, an alternative mechanism for requesting funding and monitoring (e.g. clinical audit) will be agreed with commissioners.

Trusts are required to obtain ICB funding for the use of bDMARDs and tsDMARDs in the management of rheumatoid arthritis via Blueteq (or an agreed alternative) prior to starting therapy and for continuation of therapy as described on the Blueteq forms.

References

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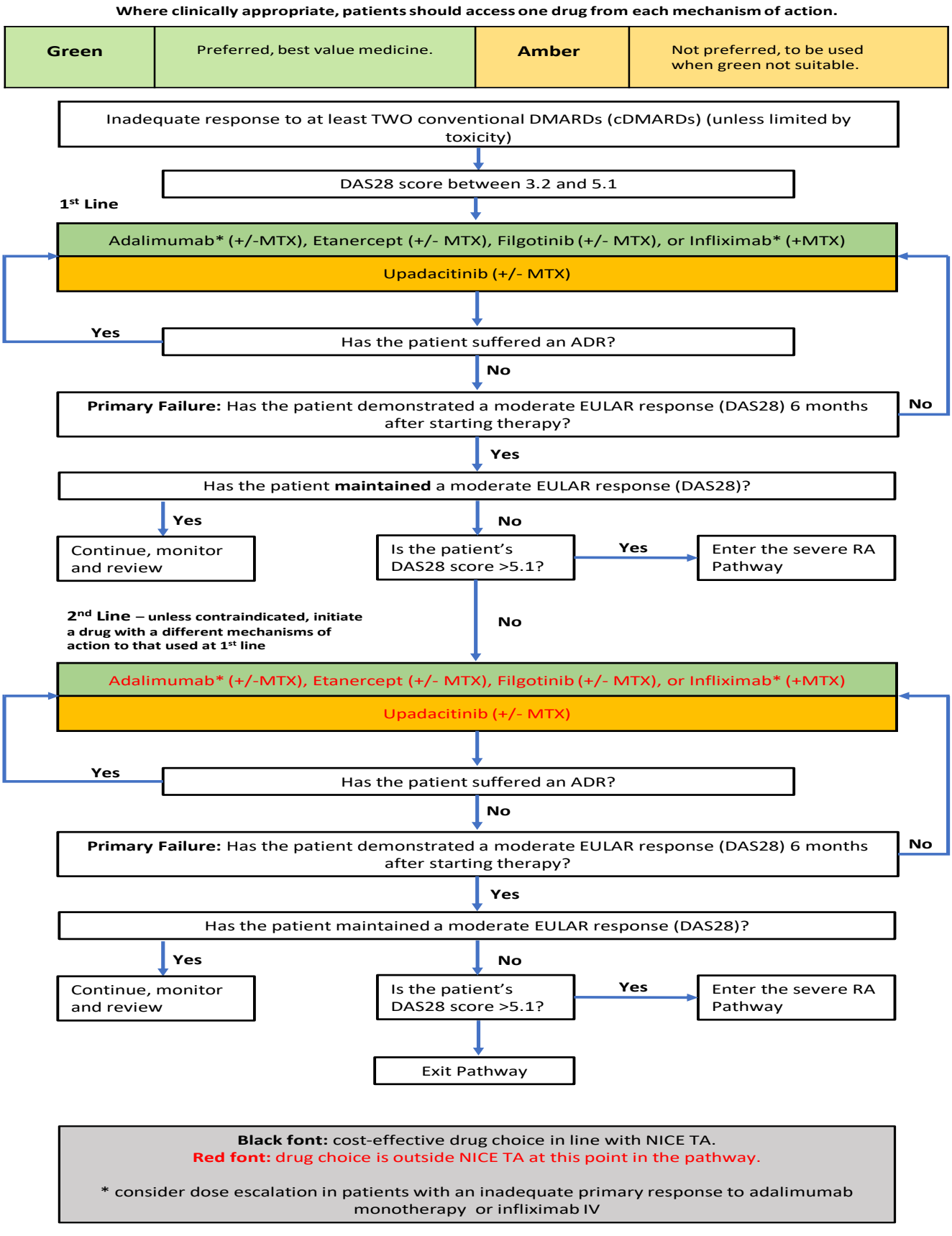
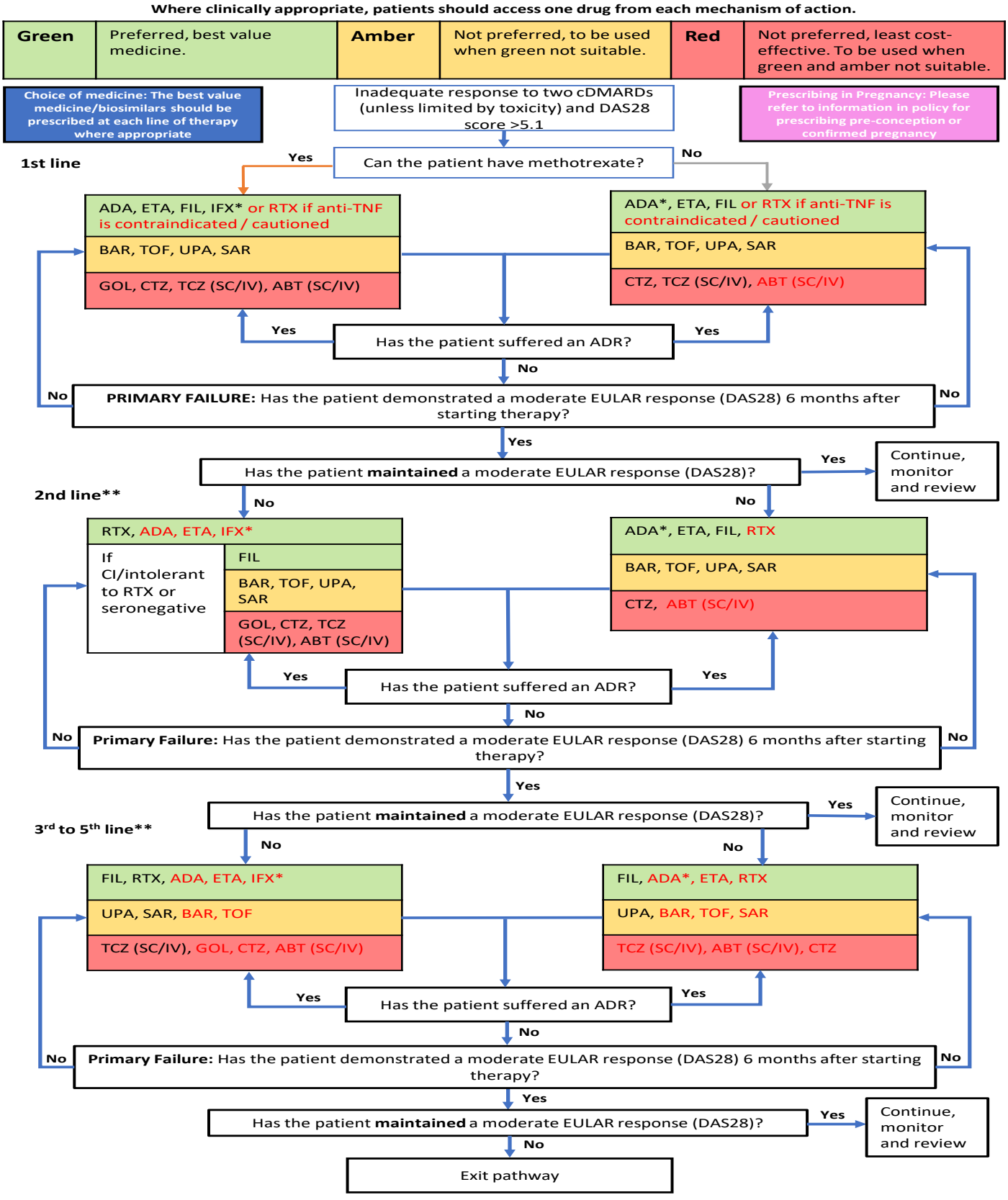
Appendix 1. Biologic Treatment Pathway: Moderate disease



Appendix 2. Biologic Treatment Pathway: Severe disease



*consider dose escalation in patients with an inadequate primary response to adalimumab monotherapy or infliximab IV
**Choose a drug with a different mechanism of action at each line
Red font: drug choice is outside NICE TA and/or off-label at this point in the pathway.

Appendix 3. Drug factors to consider (including mechanisms of action)

The table below provides a cost effectiveness guide for each biologic based upon first year of therapy, with the loading dose schedule taken into consideration. The cost will vary depending upon commercial arrangements and access to short-term free of charge supplies, which has not been taken into consideration for this guidance.

Mechanism of Action	Drug Name	Indicated for	TA (other indications)	Drug cost
Anti-TNFα	Adalimumab (biosimilar)	Moderate disease DAS score ≥3.2 and Severe disease DAS score >5.1 after conventional treatment has failed.	TA146 - Psoriasis TA187 - Crohn's TA199 - Psoriatic arthritis TA329 - Ulcerative colitis TA373 - JIA TA383 – Ankylosing spondylitis and non-radiographic axial spondylitis TA392 - Hidradenitis suppurativa TA455 - Psoriasis TA460 – Non-infectious uveitis	£
	Etanercept (biosimilar)	Moderate disease DAS score ≥3.2 and Severe disease DAS score >5.1 after conventional treatment has failed.	TA103 - Psoriasis TA199 – Psoriatic arthritis TA373 – JIA TA383 – Ankylosing spondylitis and non-radiographic axial spondylitis TA455 - Psoriasis	£
	Infliximab (biosimilar)	Moderate disease DAS score ≥3.2 and Severe disease DAS score >5.1 after conventional treatment has failed.	TA134 - Psoriasis TA163 – Ulcerative colitis (acute) TA187 – Crohn's TA199 – Psoriatic arthritis TA 329 - Ulcerative colitis TA383 – Ankylosing spondylitis and non-radiographic axial spondylitis	£
	Certolizumab	Severe disease DAS28 score >5.1 after conventional treatment has failed.	TA383 – Ankylosing spondylitis and non-radiographic axial spondylitis TA445 – Psoriatic arthritis TA574 - Psoriasis	£££
	Golimumab	Severe disease DAS28 score >5.1 after conventional treatment has failed.	TA220 – Psoriatic arthritis TA497 – Non-radiographic axial spondyloarthritis TA329 - Ulcerative colitis	£££

Mechanism of Action	Drug Name	Indicated for	TA (other indications)	Drug cost
JAKi	Filgotinib	DAS28 score ≥3.2 after conventional treatment has failed.	TA792 – Ulcerative colitis	£
	Baricitinib	DAS28 score >5.1 after conventional treatment has failed.	TA681 – atopic dermatitis	££
	Tofacitinib	DAS28 score >5.1 after conventional treatment has failed.	TA375 – JIA TA547 – Ulcerative colitis TA543 – Psoriatic arthritis	££
	Upadacitinib	DAS28 score ≥3.2 after conventional treatment has failed.	TA768 – Psoriatic arthritis TA814 – Atopic dermatitis TA829 – Ankylosing spondylitis TA856 – Ulcerative colitis TA861 – Non-radiographic axial spondyloarthritis TA905 – Crohn's disease	££
IL-6 inhibitor	Sarilumab	DAS28 score >5.1 after conventional treatment has failed.	None	££
	Tocilizumab	DAS28 score >5.1 after conventional treatment has failed.	TA238 – JIA TA373 - JIA TA518 – Giant cell arteritis TA878 – COVID-19	£££
CD20 inhibitor	Rituximab	DAS28 score >5.1 after conventional treatment and at least one anti-TNF.	TA137 – Relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma TA174 - Chronic lymphocytic leukaemia TA193 – Relapsed or refractory chronic lymphocytic leukaemia TA226 – Follicular non-Hodgkin's lymphoma TA243 – Stage III-IV follicular lymphoma TA308 – Anti-neutrophil cytoplasmic antibody-associated vasculitis TA561 – Chronic lymphocytic leukaemia TA627 – Follicular lymphoma TA649 – Relapsed or refractory diffuse large B-cell lymphoma	£

Mechanism of Action	Drug Name	Indicated for	TA (other indications)	Drug cost
Fusion Protein	Abatacept	DAS28 score >5.1 after conventional treatment has failed.	TA373 – JIA	**£££**

Appendix 4. 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)
FIL	Filgotinib (JAK inhibitor)
GOL	Golimumab (anti-TNF)
IFX	Infliximab (anti-TNF)
MTX	Methotrexate (conventional DMARD)
RTX	Rituximab (CD20 inhibitor)
SAR	Sarilumab (IL-6 inhibitor)
TCZ	Tocilizumab (IL-6 inhibitor)
TOF	Tofacitinib (JAK inhibitor)
UPA	Upadacitinib (JAK inhibitor)