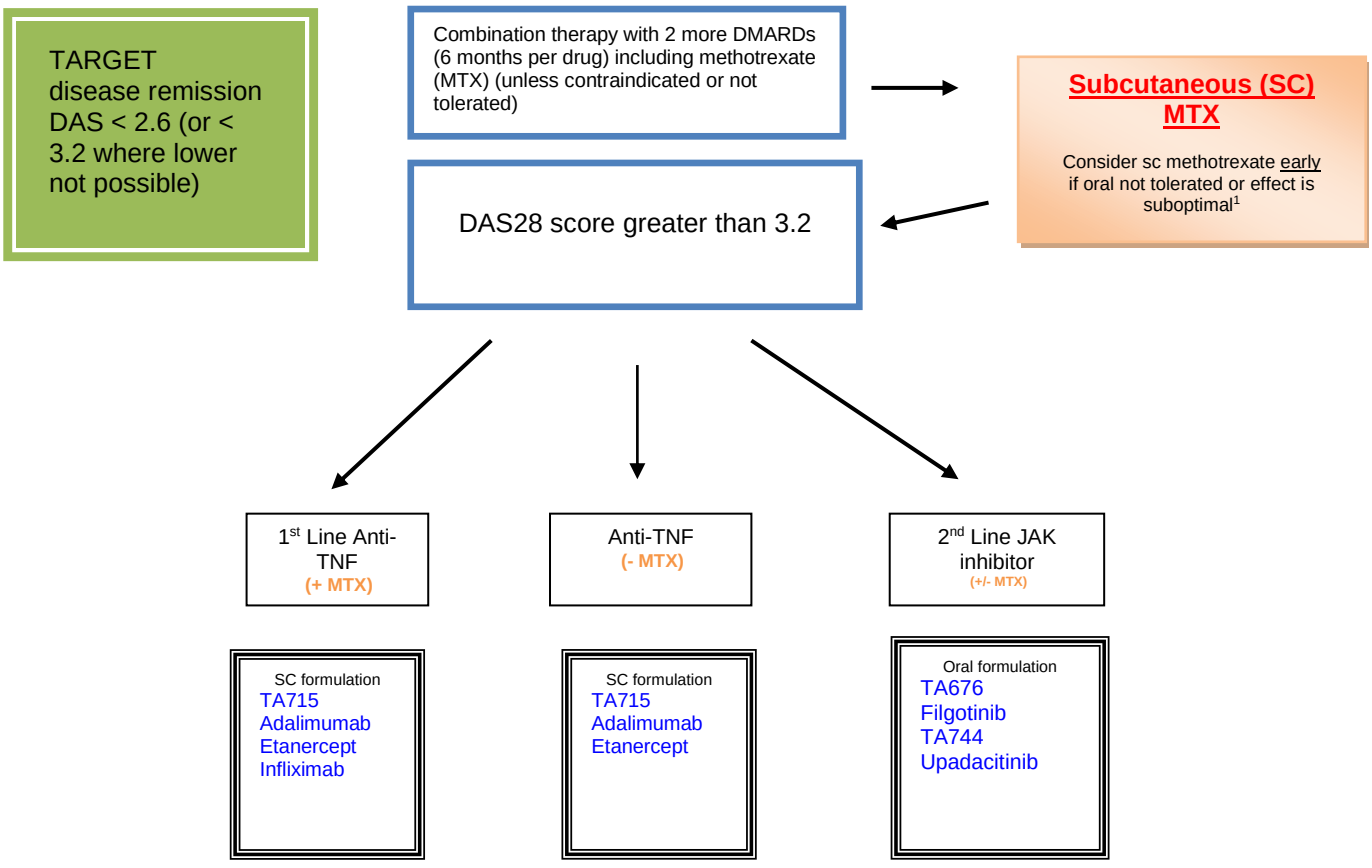
NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

Biologics and JAK inhibitor pathway for moderate and severe rheumatoid arthritis

Biologics Pathway in MODERATE RA (TA676, TA715 and TA744)
(Created Oct 2021, Updated Feb 2022)



Patient tolerates **and** improvement in DAS28 by >0.6 points by 6 months

An alternative may be considered in case of adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

Yes → Continue treatment. 6 monthly monitoring

Non responders to first biologic – evaluation of risks/benefits – consider alterative TNFi or move to 2nd line JAKi

Patient tolerates **and** improvement in DAS28 of >0.6 points by 6 months?

Yes → Continue treatment. 6 monthly monitoring

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Biologics Pathway in Severe RA (TA375, TA195, TA225, TA415, TA466, TA247, TA480, TA485,TA665, TA676) (Updated October 2021; Review May 2022)

TARGET disease remission DAS < 2.6 (or < 3.2 where lower not possible)

Combination therapy with 2 DMARDs (6 months per drug) including methotrexate (MTX) (unless contraindicated)

Subcutaneous (SC) MTX

Consider sc methotrexate early if oral not tolerated or effect is suboptimal[1]

DAS28 score greater than 5.1

MTX not tolerated or contraindicated (including SC MTX)

Choose most appropriate agent and if no clear indication for a specific agent, then use the least expensive drug (please liaise with pharmacy)
Where both SC and intravenous (IV) formulations are available, SC is recommended 1st line. IV can be used if clinician feels this is most appropriate after evaluation of patient factors (page 2)

Anti-TNF (with MTX)

Etanercept
Infliximab
Golimumab
Adalimumab
Certolizumab pegol

T-Cell (with MTX)

Abatacept

SC alternative is available (consider instead of IV)

Anti-IL-6 (with MTX)

Sarilumab

Tocilizumab

May be most expensive 1st line option if given by IV, depending on administration costs.
SC alternative is available (consider instead of IV)

Anti B-cell (+/- MTX)

Rituximab

Consider first line especially if:
-Recent history of lymphoma
-Latent TB with contraindications to the use of chemoprophylaxis
-Previous history of demyelinating disease
-Treated solid malignancy within last< 5-10 years
-Felty's syndrome
-Overlap syndrome SLE/RA
- Multiple sclerosis

JAK inhibitor (+/- MTX)

Oral formulation
Filgotinib
Upadacitinib
Baricitinib (RA-BEAM trial)
Tofacitinib**

** Consider tofacitinib in patients with severe (creatinine clearance <30 mL/min) renal impairment or on haemodialysis as per SPC.

Monotherapy

Head-to-head TCZ vs ADA monotherapy shows superiority of TCZ.
(ADACTA trial)

Upadacitinib
Filgotinib
Baricitinib
Etanercept
Abatacept#
Tocilizumab#
Adalimumab
Certolizumab pegol
Sarilumab
**Tofacitinib (See MHRA warning)

#s/c recommended 1st line rather than IV
See comments for combination therapy.

Patient tolerates and improvement in DAS 28 of ≥1.2 points by 6 months?
An alternative TNF-α inhibitor may be considered for in case of adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.

Yes

Continue treatment.
6 monthly monitoring

Non responders to first biologic (evaluation of risks/benefits on individual basis)*

Anti-TNF non -responder

If rituximab withdrawn due to adverse events; is contra-indicated and in all sero-negative patients

Monotherapy

Head-to-head TCZ vs ADA monotherapy shows superiority of TCZ.
(ADACTA trial)

Upadacitinib
Filgotinib
Baricitinib
Etanercept
Abatacept
Tocilizumab
Adalimumab
Certolizumab pegol
Sarilumab
**Tofacitinib

Sero-positive only: Rituximab (with MTX)

Dose no more frequently than every 6 months

(With MTX): Abatacept

SC alternative is available (consider instead of IV)

(With MTX):

Etanercept
Infliximab
Golimumab
Adalimumab
Certolizumab pegol

(+/- MTX): Sarilumab / Tocilizumab

SC alternative is available (consider instead of IV)

(+/- MTX):

Oral formulation
Upadacitinib
Filgotinib
Baricitinib
(RA-BEAM trial)
Tofacitinib**

Patient tolerates and there is improvement in DAS 28 of 1.2 points or more by 6 months?

Yes

Continue treatment.
6 monthly monitoring

No

Evaluation of risks/benefits on individual basis *

*Evidence of safety/efficacy not currently available and therefore careful consideration of risks/benefits required on an individual basis for:

1. Anti-TNF or abatacept after toclizumab
2. Anti-TNF or tocilizumab after abatacept
3. Rituximab after toclilizumab or abatacept
4. Abatacept after rituximab
5. JAKI before biologics/biosimilars

Certolizumab can be prescribed after anti-TNF failure (TA 415)
There is also limited evidence for use of tocilizumab after rituximab, but this has been recognised by NICE as appropriate (see TA 247)

Biologics pathway in Rheumatology Arthritis

SC methotrexate (MTX):
Prior to commencing a biologic/biosimilar/synthetic DMARD, consider subcutaneous methotrexate, this can be offered either via shared care or homecare, depending on local arrangements.

a. SC MTX is significantly more effective[22] than oral MTX at the same dosage with no increase in side effects.
b. Routine use of SC MTX following oral MTX failure has the potential to provide considerable cost savings[23] through optimised use of MTX first line therapy.
c. Option if patient experiences gastrointestinal side effects with oral methotrexate.

Contraindications and cautions for use of biologics, biosimilars, JAKI and synthetic DMARDs:

1. With all biologics, biosimilars, JAKI and synthetic DMARDs there may be a generalised increased risk of infection, including reactivation of hepatitis B, herpes zoster and TB.
2. Anti-TNF alpha drugs can be associated with an increased risk of melanoma and non-melanoma skin cancers. Education about sun protection and monitoring of skin lesions should be offered to every patient. Severe heart failure and demyelinating disease (including multiple sclerosis) are contraindications for the use of TNF inhibitors.
3. Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis, because of the risk of gastrointestinal perforation.
4. In specific circumstances such as interstitial lung disease (ILD) careful assessment prior to treatment, systemic subsequent monitoring and respiratory opinion is advised regardless of treatment choice.
5. JAK inhibitors have a higher risk of herpes zoster infection than other biologics .MHRA warning on Tofacitinib October 2021
6. There is some evidence that some of the JAK inhibitors may increase thromboembolic (TE) risk; please assess risk factors prior to starting and use with caution in people at risk (risk factors include but are not limited to: previous TE events, obesity, smoking, diabetes, sedentarism/immobility, age > 65 years, family history of TE events).

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

Biologic/Biosimilar	Advice
ABATACEPT:	Consider if injection site reactions to anti-TNFs[1] (Level 1b evidence, Grade of recommendations B) Consider if previous hospitalised infection on anti-TNFs/potential serious infection risk[2-4] (Level III evidence, Grade of recommendation C) The efficacy is increased in patients with high levels of anti-CCP antibodies and high levels of pain[25]. Consider if co-existent ILD (risk of developing ILD and risk of infection may be lower)
ADALIMUMAB:	Consider if patient has extra articular features/ co-existent conditions such as: • Uveitis[5-7] (Level IIb evidence, Grade of recommendations C) • Psoriasis (TA 146) • Crohn's disease (TA 187), Ulcerative colitis[8-10] (Level Ia evidence, Grade of recommendation A)
FILGOTINIB: **UPADACITINIB:** **TOFACITINIB:** **BARICITINIB:**	JAK inhibitors with oral administration, consider in patients with severely impaired manual dexterity, needle phobia Fridge storage is not required Eliminates injection site reactions Consider in patients requiring frequent surgery (short half-life)
CERTOLIZUMAB PEGOL:	BSR recommends compatibility in pregnancy and breastfeeding after weighing potential risks versus benefits, and after discussion with the patient[26].
ETANERCEPT:	Consider if the patient has a potential risk of acquiring TB infection (Level III evidence, Grade of recommendation C) Consider in women planning a pregnancy in near future Consider if potential serious infection risk[2] (Level III evidence, Grade of recommendation D) Can be considered in patients with pre-existing hepatitis C infection[11,12] (Only after hepatology consultation; Level III evidence, Grade of recommendation C) Consider in patients requiring frequent surgery Consider if the patient has latex allergy (etancercept biosimilar (Benepali)) is latex free[24)]
GOLIMUMAB:	Consider if patient over 100kg (patient access scheme to double dose) Consider if patient has needle phobia/ compliance issues Potential patient convenience due to monthly dosing Consider in patients with co-existent ulcerative colitis[13,14] (Level Ia evidence, Grade of recommendations B)
INFLIXIMAB:	Consider if body weight <60kg (potential cost saving) Consider if compliance issues/ needle phobia/ severely impaired manual dexterity (IV infusion) Consider in patients with co-existing Crohn's disease (TA187), and ulcerative colitis (TA 163) Consider in patients with rheumatoid vasculitis[15,16] (Level IV evidence, Grade of recommendation B)
RITUXIMAB:	May be safest option in patients with a history of malignancy

Prescribing points for biologics, biosimilars, JAKI and synthetic DMARDs:

a. Every intravenous and subcutaneous biologic/biosimilar/JAKI must be prescribed by brand.
b. The brands prescribed for each biologic/biosimilar will be guided by the Trust formulary.
c. Choice of biologic should continue to be guided by patient need, patient characteristics, clinician recommendation, and local service delivery as directed by this pathway.
d. In the absence of a specific clinical need the 'most cost effective drug first' principle will apply with the pathways but cost alone will not be the only principle to guide prescribing of biologic therapies.
e. When an PO, SC and IV version of medication is available (be mindful of capacity in infusion unit and consider IV only if clinician feels this is most appropriate)
f. Consider patient factors such as latex allergies, device, and level of manual dexterity, frequency of administration, route, and adherence to drug.
g. Selected Homecare schemes include enhanced nursing support; liaise with the homecare pharmacy team for more information.

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NB: This pathway is correct at the time of publication. Any NICE Technology Appraisals which are published after this date in relation to rheumatoid arthritis (adults) will be commissioned in line with the TA implementation recommendations**.**

This pathway is approved across the Cambridgeshire and Peterborough NHS system.
Original pathway ratified at November 2017 Cambridgeshire and Peterborough CCG Joint Prescribing Group (JPG).
Updated October 2021, December 2021 and February 2022 and noted at JPG