



High cost drugs pathways for rheumatoid arthritis in adults

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Review due 2 years from publication

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DOCUMENT CONTROL

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Nov 2016	Meghna Jani	Abbreviated text prior to pathways, addition of TA415, modified content in pathways as per GMMMG working group discussions, updated formatting issues	3.2
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Approvals

This document must be approved by the following before distribution:

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High cost drugs pathways for severe and moderate rheumatoid arthritis in adults

1. Background

The pathway is intended as guidelines for the use of high cost drugs in treatment of rheumatoid arthritis (RA). It has been written using up to date published research and evidence based medicine. This pathway originated as a clinical project implemented by Manchester Academic Health Science Centre (MAHSC), a joint project between rheumatology departments at Salford Royal Hospital, Manchester University Foundation Trust and the University of Manchester, and has since extended to the Greater Manchester hospital trusts.

Currently the pathways include following classes of high cost disease-modifying anti-rheumatic drugs (DMARDs):

- biologic DMARDs (biologic agents, biologicals)
 - tumour necrosis factor (TNF) - alpha inhibitors (anti-TNFs): adalimumab, certolizumab, etanercept, golimumab, infliximab
 - fusion proteins: abatacept (CD80/86:CD28 inhibitor) and rituximab (CD20 inhibitor)
 - interleukin-6 inhibitors: sarilumab and tocilizumab
- targeted synthetic DMARDs (small molecules)
 - Janus kinase inhibitors (JAKi): baricitinib, filgotinib, tofacitinib and upadacitinib.

2. NICE guidance

Biological therapies and Janus kinase inhibitors are indicated when a patient's rheumatoid arthritis is moderate or severe and has an inadequate response to conventional disease-modifying anti-rheumatic drugs (cDMARDs), or these options are contraindicated or not tolerated.¹

Links to the relevant NICE guidelines and technology appraisals are listed below. 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. (1)

Any new high cost drugs that receive positive recommendation from NICE between this document iterations are approved for routine use within criteria specified in NICE technology appraisal and will be included in upcoming pathway updates.

[NICE All NICE products on arthritis – any guidance, advice and quality standards](#)

[NICE NG100 Rheumatoid arthritis in adults: management](#)

Management of moderate rheumatoid arthritis

In addition to treatment of severe rheumatoid arthritis, NICE has more recently approved filgotinib (February 2021), adalimumab, etanercept and infliximab (July 2021), and upadacitinib (November 2021) for use in moderate disease (DAS 3.2 to 5.1) following failure of two or more cDMARDs; for treatment algorithm see flowcharts in [sections 13-14](#).

2.1 Biologic DMARDs

- [NICE TA375 \(2016\)](#): Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed
- [NICE TA195 \(2010\)](#): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor
- [NICE TA415 \(2016\)](#): Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor
- [NICE TA225 \(2011\)](#): Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs

¹ In TA130 (October 2007), NICE defined inadequate response to conventional DMARDs, as trial of two drugs including methotrexate (unless contraindicated). A trial of a conventional DMARD was defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

- [NICE TA247 \(2012\)](#): Tocilizumab for the treatment of rheumatoid arthritis
- [NICE TA485 \(2017\)](#): Sarilumab for moderate to severe rheumatoid arthritis
- [NICE TA715 \(2021\)](#): Adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis after conventional DMARDs have failed

2.2 Targeted synthetic DMARDs

Janus kinase (JAK) inhibitors are a relatively new class of drug introduced in 2017. They are orally available disease-modifying anti-rheumatic drugs with similar efficacy to biologics. (2; 3)

- [NICE TA466 \(2017\)](#): Baricitinib for moderate to severe rheumatoid arthritis
- [NICE TA480 \(2017\)](#): Tofacitinib for moderate to severe rheumatoid arthritis
- [NICE TA665 \(2020\)](#): Upadacitinib for treating severe rheumatoid arthritis
- [NICE TA744 \(2021\)](#): Upadacitinib for treating moderate rheumatoid arthritis
- [NICE TA676 \(2021\)](#): Filgotinib for treating moderate to severe rheumatoid arthritis

3. Initiating treatment with a high cost drug

All NICE-approved high cost drugs for treatment of rheumatoid arthritis are routinely commissioned if prescribed in accordance with this pathway and used in line with criteria in the relevant NICE technology appraisal. This includes any new high cost drugs that are approved by NICE between pathway revisions.

The choice of treatment should be guided by clinical judgement, national and local guidance, and the overall value proposition offered by the individual medicines. There are numerous factors which may influence the choice of drug at each point in the pathway, including disease presentation, extra-articular manifestations, co-morbidities, dexterity, previous treatment history and adherence, route of administration, frequency, devices available. These factors should be considered in a discussion between the patient and their clinician, including the advantages and disadvantages. The rationale for choice should be documented.

Patients with other concomitant inflammatory disorders may benefit from a drug that is also indicated for this comorbidity and approved under the appropriate [GMMMG High Cost Drugs Pathway](#).

If more than one treatment is suitable, the best value product should be chosen (taking into account price per dose, dosage and treatment frequency and administration costs and biosimilar availability). At the time of this version publication this was biosimilar adalimumab. See [GMMMG \(2016\): Prescribing of high cost biosimilar biological medicines](#). Clinicians should also contact pharmacy for advice on the relative cost of these drugs. If the least expensive product is not prescribed, the reasons why must be documented made available to commissioners if requested. Records can be made on Blueteq forms where applicable.

In line with the [MHRA guidance \(2008\): Biosimilar products](#), biologics including biosimilars must be prescribed by brand name (i.e. the brand of biosimilar or originator product) to support ongoing pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new high cost drug medicine (including biosimilars and newer classes of drugs, e.g. JAK inhibitors) and additional monitoring is indicated through the MHRA's Black Triangle Scheme.

Patients should be enrolled on to the relevant registry which serves data collection on the safety and effectiveness of medicines in clinical practice. See [section 11](#) for more on registries.

Treatment should be reviewed to assess efficacy as per NICE guidance, and thereafter at least every 12 months. For treatment pathways, see flowcharts in [sections 13-14](#). For specific treatment selection criteria see table 2 in [section 12](#) lists available treatments.

4. **Biosimilars**

Use of biosimilars, including switching from originator to a biosimilar, has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The British Society for Rheumatology (BSR) have published a [biosimilar position statement](#) which states:

- When considering switching patients on a biologic originator product to a biosimilar, patients must be provided with sufficient information to make an informed decision, with the support of their rheumatology multidisciplinary team.
- No patients should be switched from one biosimilar to another biosimilar of the same originator product purely based on cost, as there are potential concerns over patient safety and immunogenicity.
- When the specific biologic prescribed is unavailable, the dispensing pharmacist must contact the prescribing clinician to seek advice as to appropriate short-term alternatives. The patient must be always informed about any discussions concerning their medicine.

Furthermore, the GMMMG advised in its statement on biosimilar, regarding changing from originator to a biosimilar (1):

- There is 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 be done after discussion and agreement with individual patients.
- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing and in discussion with the hospital pharmacy department.
- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing.

N.B. Inflectra® and Remsima® are different brands of infliximab and are marketed by different companies, but it should be noted that they are the same biosimilar (CPT-13, produced by the same manufacturer, Celltrion).

5. **Alternative dosing of high cost drugs (including dose escalation and de-escalation)**

Treatment optimisation, including dose escalation, and de-escalation, is licensed for several drugs.

For treatment initiation refer to individual drug's SPC via <https://www.medicines.org.uk/>.

For some drugs, reduced doses are indicated in the elderly, renal impairment, hepatic impairment and according to blood test results – see [section 21](#) for specific monitoring considerations and summary of product characteristics for adjusted dosing. For safety alerts recommending dose adjustments see [section 15](#).

Patients with other concomitant inflammatory disorders may benefit from dose escalation, where recommended by manufacturer or supported by other clinical evidence; see other relevant [GMMMG High Cost Drugs pathways](#) for more information.

Table 1. Standard and alternative HCD regimens (4)

Drug	Standard maintenance dose	Alternative regimes
Abatacept (IV)	500mg, 750mg, 1000mg as per body weight every 4 weeks	Not specified in the marketing authorisation
Abatacept (SC)	125mg once weekly	Not specified in the marketing authorisation
Adalimumab (SC)	40mg every 2 weeks	40mg every week, or 80mg every 2 weeks, based on adequate response, drug level and/or antibody where appropriate ²
Certolizumab pegol (SC)	200mg every 2 weeks	400mg every 4 weeks
Etanercept (SC)	50mg once weekly	25mg twice weekly
Infliximab (IV)	3mg/kg every 8 weeks	3mg/kg up to every 4 weeks OR up to 7.5mg/kg (in 1.5mg increments) up to every 8 weeks, drug level and/or antibody where appropriate
Golimumab (SC)	50mg monthly	100mg monthly, in patients >100kg who do not achieve an adequate response after 3-4 months at 50 mg

² In monotherapy. (4)

Drug	Standard maintenance dose (4)	Alternative regimes (4)
Rituximab (IV)	Two 1g doses given 2 weeks apart. Further 1g doses may be repeated at minimum 6 monthly intervals	Two 500mg doses given 2 weeks apart OR a single 1g dose. Further doses to be repeated after 6 months
Sarilumab (SC)	200mg every 2 weeks	Not specified in the marketing authorisation
Tocilizumab (IV)	8mg/kg every 4 weeks	Not specified in the marketing authorisation
Tocilizumab (SC)	162mg every week	Not specified in the marketing authorisation
JAK inhibitors		
Baricitinib (PO)	4mg once daily	2 mg once daily may be considered once sustained disease control achieved
Filgotinib (PO)	200mg once daily	Not specified in the marketing authorisation
Tofacitinib (PO)	5mg twice daily or 11mg MR once daily	Patients taking 5 mg twice daily may switch to 11 mg once daily modified release
Upadacitinib (PO)	15mg once daily	Not included in the marketing authorisation

IV – intravenous; PO - oral; SC – subcutaneous

In sustained remission, tapering of biologic agents should be considered. (5)

6. Treatment failure with a high cost drug

The available guidance recommends considering changing to an alternative high cost drug if treatment fails due to inefficacy or adverse events. (6) For the purposes of this pathway, this can include failure due to inefficacy:

- Primary failure: rheumatoid arthritis disease activity does not improve adequately to a high cost drug within the timescales defined in the marketing authorisation and NICE technology appraisal (see [section 2](#))
- Secondary failure: rheumatoid arthritis disease activity initially improves adequately within the timescales defined in marketing authorisation and NICE technology appraisal (see [section 2](#)), but the patient subsequently loses this response. Although all high cost drugs are highly efficacious in the short term, longer-term attrition is observed. In effect, changes to therapy may be required for longer term disease control for a life-long condition.

There may be other reasons for treatment discontinuation, including:

- Adverse effects resulting in reduced tolerability
- Newly identified drug safety issue during successful treatment resulting in a newly identified relative or absolute contraindication
- Patient becoming pregnant (see [section 18.2](#))

7. Sequential use of high cost drugs

Prior to switching to a subsequent treatment, consideration may be given to dose escalation where there is evidence to support safety and efficacy (see [section 5](#)), and when an inadequate primary response may be due to insufficient drug dosing. For example, in obese patients or when disease relapses during the treatment cycle.

Degree of response or lack of response to one high cost drug is not predictive of a patient's likely response to alternative agents in an alternative class, or even in the same class. (7)

High cost drugs for rheumatoid arthritis currently have several different molecular targets (e.g., TNF α , IL-6), or have varying affinity or avidity where the target is the same. Using an agent with a different mechanism of action to the failed therapy may result in regaining disease control.

Choice of subsequent agent should be made following review by a specialist with consideration given to the mechanism of action of previously used drugs, the severity and current level of disease control, the presence of co-existing conditions, as well as the patient's past medical history and with regards to contraindications and precautions to available treatment options. This should be a shared decision with the patient. See [section 3](#) for more details on factors to consider when initiating treatment with a new high cost drug.

In complex cases, it is recommended to seek advice from other professional colleagues, e.g. as a part of multi-disciplinary team discussion. Where available, specialist pharmacist should be involved in decision making.

With each new treatment, patients must meet the criteria laid out in the relevant NICE technology appraisal or otherwise stipulated in this pathway. There is no need for an individual funding request in such circumstances.

Recommendations differ on the need for a washout period when switching from one high cost drug to another. There are very little published data on this topic. The following should be considered when switching: clinical circumstances, drug levels (where appropriate), half-life of the drug (table 3 in [section 17](#)), safety (e.g. bridging with steroids) and practical considerations. Considering the above, the next drug could be started when the next dose of the previous drug was due or at least after one-half life of current drug has passed, as clinically appropriate.

Switching to the biosimilar of a successful treatment (e.g. as a part of switching programme) is not considered a sequential high cost drug use.

Repeated pre-high cost drug checks should be considered when switching to a new agent as per clinical judgement, and depending on the duration of previous therapy, the clinical picture of individual patient and relevant risk factors.

8. Data collection requirements

Patient-level information including full clinical details, e.g. disease scores at treatment initiation and assessment for continuation, previous drug history, reasons for change of treatment must be made available to commissioners. This is expected to be via Blueteq or equivalent, where commissioned.

Where available and subject to contractual arrangements Blueteq or equivalent forms which comply with this pathway should be filled in for each new high cost drug at initiation and continuation to secure funding.

Where agreed, data available from Blueteq (or equivalent) system or clinical audit may be used to monitor compliance with NICE and GMMMG pathway and for other purposes (e.g. service development or pathway extension for newly identified cohorts of patients).

9. Individual funding requests (IFR)

Individual funding request will be considered under the [GM EUR Operational Policy.pdf \(gmeurnhs.co.uk\)](#).

Exhausting the treatment options in this pathway does not automatically establish exceptionality.

10. Free of charge schemes

All free of charge schemes must be approved in accordance with trust guidance and the [GMMMG Free of Charge guidance](#). (8) Approval should be agreed at the trust's medicines management committee.

There must be clear exit criteria that do not place financial burden on commissioners and do not raise patients' expectations of continuation of treatment.

11. Research

Where available, enrolment in a suitable registry or observational clinical trial is encouraged so that specific information about these treatments in rheumatoid arthritis can be captured.

Clinicians are strongly encouraged to participate in long-term safety studies or registries such as the British Society of Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBR-RA). For more information on the BSRBR-RA visit www.bsrbr.org/. For eligibility see <https://bsrbr.org/hospitals/eligibility/>. In addition, opportunities for local observational research studies may also be considered.

Some sites host early and later phase clinical trials of novel high cost drugs. Active trials can be found on the [NIHR website](#).

12. Available drugs and factors affecting drug choice

Where multiple treatment options are clinically suitable the best value drug, all factors considered, should be chosen. See [section 3](#) for considerations regarding new drugs initiation.

Note that all bDMARDs and JAK inhibitors may increase infection risk. In some cases, e.g., interstitial lung disease, careful assessment and systemic monitoring is required, and respiratory opinion is advised. Consider oral or intravenous options if needle phobia or inability to self-administer subcutaneous injections; intravenous preparations may help address adherence issues, or severely impaired manual dexterity. For safety alerts on safety of JAK inhibitors see [section 15](#).

Biological DMARDs and JAK inhibitors should be given in combination with MTX, unless MTX is contraindicated or withdrawn due to adverse events. In specific clinical circumstances, most bDMARDs can be used as monotherapy* (non-methotrexate cDMARD or no cDMARD).

Abbreviations GMMMG RA pathway

ADAb – anti-drug antibodies	bDMARD – biological DMARD (adalimumab, etc)	ILD – interstitial lung disease	SLE – systemic lupus erythematosus
ADR – adverse drug reaction	cDMARD – conventional DMARD (methotrexate, etc)	JAK inhibitors – Janus kinase inhibitors (baricitinib, etc)	TB – tuberculosis
CRP – C-reactive protein	ESR - erythrocyte sedimentation rate	MTX – methotrexate	UC – ulcerative colitis
CCP – cyclic citrullinated peptide	HCD – high cost drug	RF – rheumatoid factor	VTE/PE – venous thromboembolism /pulmonary embolism

Table 2. Available HCDs – information to support choice

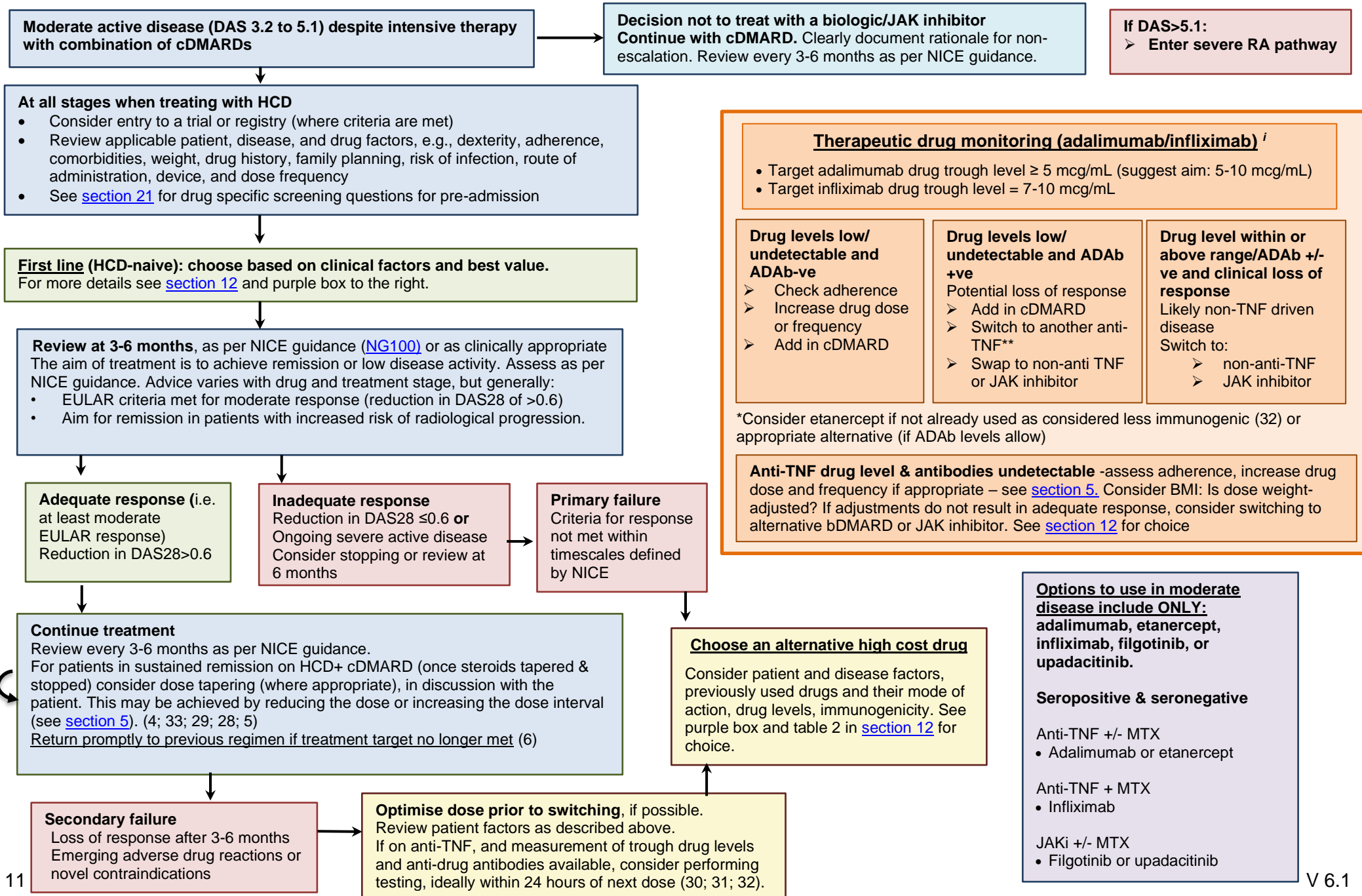
Drug	Mode of action	Route	Moderate RA	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.
Abatacept	Fusion protein	IV & SC	No	Consider first line if: ILD (9) (10) Consider if high risk of infection or previously hospitalised with infection whilst another biologic/JAK inhibitor (10) (11) Monotherapy possible, if required by clinical circumstances - off label and outside of NICE, but evidence-based (12)
Adalimumab	TNF-inhibitor	SC	Yes	Licensed & NICE-approved in psoriasis (TA146), Crohn's (TA187), UC (TA329), hidradenitis suppurativa (TA392), uveitis (TA460) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Certolizumab pegol	TNF-inhibitor	SC	No	Consider first line in women who are pregnant or breastfeeding, or who are likely to become pregnant during treatment (4) (13) Licensed in US (but not UK) for Crohn's. Some evidence for efficacy in uveitis ³ , but no licence. Monotherapy possible if required by clinical circumstances (on label and within NICE)
Etanercept	TNF-inhibitor	SC	Yes	NICE-approved in psoriasis (TA103), but not in GMMMG psoriasis pathway due to lower efficacy. Consider if anti-TNF is otherwise appropriate, but patient at risk of TB or has potential serious infection risk or previous hospitalisation for infection while on anti-TNFs (10) (11) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Infliximab	TNF-inhibitor	IV	Yes	Must be used with methotrexate (monotherapy not an option). NICE-approved in psoriasis (TA134), Crohn's (TA187), UC (TA329). Some evidence for efficacy in uveitis (but no licence) (14).

³ Based on clinical experts' opinion.

Drug	Mode of action	Route	Moderate RA	Supplementary information. This list is not exhaustive – refer to SCP for details on individual drugs.
Golimumab	TNF-inhibitor	SC	No	NICE-approved in UC (TA329). Consider for use in patients weighing >100kg (higher dose licensed in this population). Must be used with methotrexate (monotherapy not an option)
Rituximab	CD-20 inhibitor	IV	No	Consider first line if: - recent history of lymphoma/lymphoproliferative disease (10) or latent TB with contraindications for chemoprophylaxis (15) - ILD (9) (10), SLE / connective tissue disease (10) (see also NHSE policy: rituximab in SLE) - Felty's syndrome (16), rheumatoid vasculitis (10), history of demyelinating disease (15) Monotherapy possible (preferably with leflunomide), if required by clinical circumstances (off label and outside of NICE but evidence-based and recommended by BSR (17) (18))
Sarilumab	IL-6 inhibitor	SC	No	Consider if AA amyloidosis (19) Giant cell arteritis (licensed in US, but not UK). Monotherapy possible if required by clinical circumstances (on label and within NICE)
Tocilizumab	IL-6 inhibitor	IV & SC	No	Consider if AA amyloidosis (19) (20) NICE-approved in giant cell arteritis (TA518) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Baricitinib	JAK inhibitor	PO	No	NICE-approved in atopic dermatitis (TA681) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Filgotinib	JAK inhibitor	PO	Yes	NICE-approved in UC (TA792) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Tofacitinib	JAK inhibitor	PO	No	NICE-approved in psoriatic arthritis (TA543) and UC (TA547) Monotherapy possible if required by clinical circumstances (on label and within NICE)
Upadacitinib	JAK inhibitor	PO	Yes	NICE-approved in psoriatic arthritis (TA768) and UC (TA856) Monotherapy possible if required by clinical circumstances (on label and within NICE)

*Monotherapy as used in NICE technology appraisals, i.e. without MTX and with/without non-MTX cDMARD (e.g. leflunomide)

13. GM HCD Pathway for moderate rheumatoid arthritis (DAS 3.2 to 5.1)



If DAS>5.1:
 ➤ Enter severe RA pathway

Therapeutic drug monitoring (adalimumab/infliximab) ⁱ

- Target adalimumab drug trough level ≥ 5 mcg/mL (suggest aim: 5-10 mcg/mL)
- Target infliximab drug trough level = 7-10 mcg/mL

<p>Drug levels low/ undetectable and ADAb-ve</p> <ul style="list-style-type: none"> ➤ Check adherence ➤ Increase drug dose or frequency ➤ Add in cDMARD 	<p>Drug levels low/ undetectable and ADAb +ve</p> <p>Potential loss of response</p> <ul style="list-style-type: none"> ➤ Add in cDMARD ➤ Switch to another anti-TNF** ➤ Swap to non-anti TNF or JAK inhibitor 	<p>Drug level within or above range/ADAb +/-ve and clinical loss of response</p> <p>Likely non-TNF driven disease</p> <p>Switch to:</p> <ul style="list-style-type: none"> ➤ non-anti-TNF ➤ JAK inhibitor
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*Consider etanercept if not already used as considered less immunogenic (32) or appropriate alternative (if ADAb levels allow)

Anti-TNF drug level & antibodies undetectable -assess adherence, increase drug dose and frequency if appropriate – see section 5. Consider BMI: Is dose weight-adjusted? If adjustments do not result in adequate response, consider switching to alternative bDMARD or JAK inhibitor. See section 12 for choice

Options to use in moderate disease include ONLY: adalimumab, etanercept, infliximab, filgotinib, or upadacitinib.

Seropositive & seronegative

Anti-TNF +/- MTX

- Adalimumab or etanercept

Anti-TNF + MTX

- Infliximab

JAKi +/- MTX

- Filgotinib or upadacitinib

14. GM HCD Pathway for severe rheumatoid arthritis (DAS28 > 5.1)

Active disease despite intensive therapy with combination of cDMARDs DAS>5.1

At all stages when treating with HCD

- Consider entry to a trial or registry (where criteria are met)
- Review applicable patient, disease, and drug factors, e.g., dexterity, adherence, comorbidities, weight, drug history, family planning, risk of infection, route of administration, device, and dose frequency
- See [section 21](#) for drug specific screening questions for pre-admission

First line (HCD-naive): choose based on clinical factors and best value.

For more details see [section 12](#) and purple box to the right.

Review at 3-6 months, as per NICE guidance ([NG100](#)) or as clinically appropriate

The aim of treatment is to achieve remission or low disease activity. Advice varies with drug and treatment stage, but generally:

- Reduction in DAS28 of ≥ 1.2 or EULAR criteria met
- Aim for remission in patients with increased risk of radiological progression.

Adequate response

Reduction in DAS28 of ≥ 1.2
or
EULAR criteria met - and
minimal active disease

Moderate response

Reduction in DAS28 0.6-1.1
or
reduction in DAS28 of ≥ 1.2
but ongoing active disease

Inadequate response

Reduction in DAS28
< 0.6 or
Ongoing severe
active disease.

Primary failure

Criteria for
response not met
within timescales
defined by NICE

Review every 3-6 months as per NICE guidance

If non-adequate response, decision to continue with treatment will depend on clinical judgement and shared decision making with patients.
For patients in sustained remission on biologic + cDMARD (once steroids tapered & stopped) consider dose tapering (where appropriate), in discussion with the patient. This may be achieved by reducing the dose or increasing the dose interval (see [section 5](#)). (4; 33; 29; 28; 5)
Return promptly to previous regimen if treatment target no longer met (6)

Choose an alternative high cost drug

Consider patient and disease factors, previously used drugs and their mode of action, drug levels, immunogenicity. See table 2 in [section 12](#) for choice.

Secondary failure

Loss of response after
3-6 months
Emerging adverse drug
reactions or novel
contraindications

Optimise dose prior to switching, if possible.

Review patient factors as described above.
If on anti-TNF and measurement of trough drug levels and anti-drug antibodies available, consider performing testing, ideally within 24 hours of next dose (30; 31; 32).

For therapeutic drug monitoring
(adalimumab/infliximab)

➤ see previous page ([section 13](#))

Consider presence of CCP & RF antibodies, when assessed.

For more details on drug choice see table 2 in [section 12](#)

If seropositive, consider with MTX:

- Anti-TNF
- Rituximab
- Abatacept
- Tocilizumab/sarilumab
- JAK inhibitor

If seronegative, consider with MTX:

- Anti-TNF
- Tocilizumab/sarilumab
- JAK inhibitor
- Rituximab/abatacept (if no suitable alternatives)

Biological DMARDs and JAK inhibitors should be given in combination with MTX, unless MTX is contraindicated or withdrawn due to adverse events. In specific clinical circumstances, most bDMARDs can be used as monotherapy (non-methotrexate cDMARD or no cDMARD). See table 2 for details.

If MTX contraindicated or not tolerated after an appropriate trial, and only in specific clinical circumstances, consider monotherapy with:

- Anti-TNF (but not infliximab or golimumab)
- Tocilizumab/sarilumab (if symptoms of IL-6-mediated disease)
- Rituximab with a non-MTX cDMARD (preferably leflunomide) or no-cDMARD
- Abatacept monotherapy

15. Contraindications, special warnings and precautions

15.1. Cautions and contraindications

Cautions, contraindications, and special warnings to use of systemic agents for rheumatoid arthritis are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients. For further guidance, see the [BSR biologic DMARD safety guidelines in inflammatory arthritis \(2019\)](#) or most up to date guidance.

It is important that clinical teams regularly identify patient cohorts affected by new and existing safety alerts. Review of appropriateness of continuing or changing treatment should be assessed on case-by-case basis and allowing shared decision making.

15.2. Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway. Visit www.gov.uk/drug-safety-update for up-to-date information on safety issues.

- [Janus kinase \(JAK\) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality \(2023\)](#).
In clinical trials of patients with RA, an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality, was observed in patients treated with some JAK inhibitors, particularly tofacitinib, when compared to those treated with anti-TNFs.
 - It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current or past long-term smoking and other risk factors for cardiovascular disease or malignancy.
 - JAK inhibitors should be used in caution if prescribing in patient with any risk factors for VTE. Lower doses should be use where specified the individual [summaries of products characteristics](#).
 - Incidence of non-melanoma skin cancer was higher in tofacitinib trials when compared with anti-TNFs. Therefore, periodic skin examinations for signs of skin malignancy is recommended in all patients on JAK inhibitors. Inform patients of these risks and key signs and symptoms that could warrant urgent medical attention.As indicated in 15.1, appropriateness of continuing or changing treatment in the context of the above guidance should be assessed on a case-by-case basis and with shared decision making.
- [Tofacitinib \(Xeljanz▼\): new measures to minimise risk of major adverse cardiovascular events and malignancies \(2021\)](#). Tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular risk (such as diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments.
- [Tofacitinib \(Xeljanz▼\): new measures to minimise risk of venous thromboembolism and of serious and fatal infections \(2020\)](#). Maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism unless there is no suitable alternative treatment. Due to risk of serious and fatal infections, healthcare professionals are advised only to use tofacitinib in patients older than age 65 years if there is no alternative treatment.
- [Baricitinib \(Olumiant▼\): risk of venous thromboembolism \(2020\)](#). Discontinue baricitinib treatment permanently if clinical features of deep vein thrombosis or pulmonary embolism occur. Prescribers are reminded to use caution if using baricitinib in patients with risk factors for deep vein thrombosis or pulmonary embolism in addition to rheumatoid arthritis.
- [Tocilizumab \(RoActemra\): rare risk of serious liver injury including cases requiring transplantation \(2019\)](#). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be measured before starting treatment with tocilizumab and monitored every 4–8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Serious liver injury has been reported on treatment with tocilizumab from 2 weeks to more than 5 years after initiation.
- [Live attenuated vaccines: avoid use in those who are clinically immunosuppressed \(2016\)](#)
- [Tumour necrosis factor alpha inhibitors \(2014\)](#). Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.

- [Rituximab: progressive multifocal leukoencephalopathy in a patient](#) (2014). A case of progressive multifocal leukoencephalopathy (PML) with a fatal outcome was reported in a patient with rheumatoid arthritis who had not previously received treatment with methotrexate or a TNF antagonist.

15.3. Malignancy

The use of rheumatology high cost drugs in patients with a history of malignancy should involve a detailed discussion with the patient around the risks and benefits of treatment and consideration should be given to involving their oncologist. If a cancer occurs during treatment with a high cost drug, oncologist advice on treatment might be sought.

16. Pre-high cost drug screening

A checklist template is provided at the end of the document ([section 20](#)) and can be adapted locally if necessary.

16.1. Tuberculosis (TB)

Interferon gamma (gIFN) testing is recommended prior to commencing biologic/JAK treatment if available. Parts of Greater Manchester are identified as areas of high-risk for tuberculosis. In patients with high index of suspicion or risk of tuberculosis consider referring to previously published algorithms for additional screening (22) and referral for a respiratory opinion if deemed necessary: See NICE guideline [NG33, Tuberculosis \(Sept 2019\)](#), for further information.

With anti-TNF therapy, risk of tuberculosis reactivation appears lowest in etanercept compared to monoclonal antibodies (infliximab and adalimumab). (10) 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 are currently lacking. (10)

16.2. Hepatitis B & C

Screening for hepatitis B and C is recommended for all patients starting a biologic and JAK inhibitors, This is particularly relevant to rituximab (see: MHRA Drug Safety Update (Dec 2013) [Rituximab: screen for hepatitis B virus before treatment](#)). Screening should include: (10)

- Hepatitis B: screen for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc, HBcAb), followed by HBV DNA test if HBsAg or anti-HBc are positive.
- Hepatitis C: screen for anti-hepatitis C antibodies. If test is positive, hepatitis C RNA or core antigen assays should be performed.

If either hepatitis B or hepatitis C infection is suspected, discuss with a hepatologist. Treatment with a biological DMARD may be appropriate but should follow a risk/benefit decision made with a hepatologist, infectious disease or another relevant specialist.

16.3. Human immunodeficiency virus (HIV)

Screening for HIV is recommended for all patients starting a biologic and JAK inhibitors. NICE Quality Standard QS157 (Sept 2017) recommends young people and adults are offered HIV testing when admitted to hospital in areas of extremely high HIV prevalence, or when having a blood test when admitted to hospital in areas of high HIV prevalence. Greater Manchester is an area of high and extremely high HIV prevalence. [The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis](#) recommends risk factors for HIV infection should be documented prior to commencing a biologic and, if present, an HIV test should be performed. If considering the use of a biologic or a JAK therapy in HIV positive patients, this should be discussed with an HIV specialist.

17. Surgery and perioperative risk

Potential benefit of reduced risk of post-operative infections by stopping treatment should be balanced against risk of flare in disease activity. For most high cost drugs consideration should be given to planning surgery when at least one dosing interval has elapsed for that specific drug.

For higher risk procedures consider stopping 3–5 half-lives (if this is longer than one dosing interval) before surgery. (10)

In all cases rheumatology consultant should be involved. High cost drugs should be recommenced after surgery when there is evidence of wound healing (typically around 14 days), all sutures and staples are out, and there is no evidence of infection. For further guidance, see [The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis](#) or review trust perioperative guidelines where applicable.

Table 3. Peri-operative supportive information (4) (10) (23)

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last drug dose administered)	One mean half-life	Five half-lives
Abatacept IV	Monthly	Week 5	14 days	70 days
Abatacept SC	Every week	Week 2	14 days	70days
Baricitinib	Once daily	Day 4*	13 hours	3 days
Adalimumab	Every 2 weeks	Week 3	14 days	70 days
Certolizumab pegol	Every 2 weeks	Week 3	14 days	70 days
	Every 4 weeks	Week 5		
Etanercept	Weekly or twice weekly	Week 2	3 days	15 days
Filgotinib	Once daily	Day 5**	19 hours	4 days
Golimumab	Every 4 weeks	Week 5	14 days	70 days
Infliximab IV	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9 days	45 days
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4-7	18 days	90 days
Sarilumab SC	Every 2 weeks	Week 3***	21 days	105 days
Tocilizumab IV	Every 4 weeks	Week 5	11 days	55 days
	4mg/kg 8mg/kg		13 days	65 days
Tocilizumab SC	Every week	Week 3	13 days	65 days
Tofacitinib	Twice daily	Day 4*	3 hours	15 hours
Tofacitinib MR	Once daily	Day 4*	6 hours	30 hours
Upadacitinib	Once daily	Day 4*	14 hours	3 days

*Tofacitinib is rapidly eliminated but treatment effects do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life (4). Although not stated in summary of product characteristics this may be applicable to all JAK inhibitors due to mechanism of action. Prescribers may wish to consider longer time to surgery, i.e. Week 2.

**No published guidance available, recommendation based on half-life (4) or dosing interval (10).

***No published guidance available; recommendation based on dosing interval (10). Prescribers may also wish to consider time to surgery of Week 4 based on half-life (4).

18. Fertility, pregnancy, and lactation

Prescribers should be mindful that evidence base evolves and to use the most up to date national guidance if in doubt. At the time of writing, the [BSR pregnancy and breastfeeding guideline](#) renewed in October 2022 was based on most up to date evidence and should be referred to in first instance. Where data is not available (e.g. for newer drugs), manufacturers' recommendations may be taken into consideration.

18.1. Fertility and conception

Medicines included in this pathway may affect fertility and conception. Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks after

treatment has stopped (see table 4 in [section 18.2](#)). **Paternal exposure to high cost drugs included in this pathway is compatible with pregnancy.** (13)

When giving family planning advice, the clinician should consider the half-life of the drug in use, advice on length of contraception after the last dose, and existing evidence for use in pregnancy and breastfeeding.

18.2. Pregnancy

Among biologics, anti-TNFs, can be considered during pregnancy. The BSR (13) advise that:

- Women stable on anti-TNF therapy with known placental transfer (adalimumab, infliximab, golimumab) do not need to be switched to an anti-TNF with established minimal placental transfer (certolizumab) before or during pregnancy.
- Certolizumab due to no to minimal rate of transplacental transfer, can be considered for use thorough pregnancy.
- Patients who stop anti-TNF therapy during pregnancy may, if needed, be re-loaded as soon as possible after delivery to manage maternal disease, given infection or other complications of postpartum are excluded, and regardless of breastfeeding status.
- Lower grade, limited evidence is available for non-anti-TNFs and other biologics and is insufficient to recommend for use in pregnancy, unless there are no alternatives to control severe disease.
- JAK inhibitors are contraindicated and should be stopped at least two weeks before conception and should not be used during breastfeeding.

No studies of sarilumab, upadacitinib and baricitinib were identified in the guidance review; filgotinib was not included in evidence searches.

The decision to continue treatment in pregnancy needs to be individualised, considering all relevant factors (e.g., alternative therapies, the severity of the mother's condition prior to therapy, the risk of a disease flare caused 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.

The following table contains advice from BSR and also lists manufacturers' recommendations on time to continue contraception after treatment cessation and compatibility with pregnancy trimesters.

For stopping biologics in pregnancy to enable infant vaccinations per UK schedule see [section 18.4](#).

Table 4. Peri-conception and pregnancy compatibility

Drug	Time to continue contraception after treatment cessation [SPCs] (4)	Compatibility with trimesters [BSR 2022] (13)		
		Peri- conception	First	Second/ Third
Abatacept	14 weeks	Consider stopping at conception**	Severe disease if no alternatives	Severe disease if no alternatives
Adalimumab	5 months	Yes	Yes	Yes
Certolizumab	5 months	Yes	Yes	Yes
Etanercept	3 weeks	Yes	Yes	Yes
Golimumab	6 months	Yes	Yes	Yes
Infliximab	6 months	Yes	Yes	Yes
Rituximab	12 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Sarilumab	3 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Tocilizumab	3 months	Consider stopping at conception**	Severe disease if no alternatives**	Severe disease if no alternatives
Baricitinib*	1 week	Stop ≥2 weeks pre-conception	No	No
Filgotinib*	1 week	Stop ≥2 weeks pre-conception	No	No
Tofacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No
Upadacitinib*	4 weeks	Stop ≥2 weeks pre-conception	No	No

* However, as effects of JAK inhibitors may persist after drug elimination, a waiting period of one menstrual cycle before conception is advised.

** May be considered to manage severe maternal disease if no other pregnancy-compatible drugs are suitable.

Further information to support decision-making is available from:

- [BSR guidance on prescribing of drugs in pregnancy and lactation](#)
- Summaries of product characteristics (www.medicines.org.uk)
- UK Teratology Information Service (UKTIS) at <https://uktis.org> or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (<https://uktis.org/surveillance/reporting-an-exposure-in-pregnancy/>). UKTIS are commissioned by the UK Health Security Agency (formerly Public Health England) to perform national surveillance of known and emerging human teratogens across the UK. Advice and risk assessment for individual patients may also be available by contacting a local medicines information service via hospital pharmacy departments.

18.3. Breastfeeding

Biologics in general, and in particular anti-TNFs, are considered compatible with breastfeeding. The BSR (13) advise that:

- Anti-TNFs are compatible with breastfeeding.
- Non-anti-TNF biologics are compatible with breastfeeding (based on limited evidence).
- JAK inhibitors should be avoided in breastfeeding.

Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot always be excluded. A decision on whether to breastfeed and continue or discontinue therapy should be made considering the benefit of breastfeeding to the child and the benefit of woman.

Further information to support decision-making may be available from:

- [BSR guidance on prescribing of drugs in pregnancy and lactation](#)
- Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk
- Summaries of product characteristics (www.medicines.org.uk)
- Local medicines information service via hospital pharmacy departments.

18.4. Vaccination of infants exposed to drugs due to maternal treatment

Immunisation schedules in infants after in utero exposure to biologics will depend on timing of exposure, bioavailability and persistence of the drug, mechanism of action of the drug, and live vaccine. (13) The BSR recommend that:

- Women considered to have low risk of disease flare on withdrawal of anti-TNF in pregnancy could stop infliximab at 20 weeks, adalimumab and golimumab at 28 weeks and etanercept at 32 weeks so that a full-term infant may receive the normal UK vaccination schedule, including rotavirus vaccine at 8 weeks.
- Adalimumab, etanercept, infliximab or golimumab may be continued throughout pregnancy, to maintain disease control. In such case, immunisation with live vaccines should be avoided until infants are 6 months of age.
- Exposure to certolizumab in utero does not require any changes to vaccination schedule.

Table 5. Pregnancy exposure and impact on infant live vaccines schedule (13)

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Abatacept	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Adalimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Certolizumab	No adjustment to vaccination including live vaccines needed.
Etanercept	If stopped by 32 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Golimumab	If stopped by 28 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Infliximab	If stopped by 20 weeks, full term infant can have a normal vaccination schedule. If used till term, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Rituximab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
Sarilumab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.

Drug	Pregnancy exposure and impact on infant live vaccines schedule
Tocilizumab	If used in third trimester, avoid live vaccinations in infant vaccination schedule until 6 months of age.
JAK inhibitors	Not applicable. Contraindicated in pregnancy.

The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (24)

- BCG for tuberculosis – variation across the country depending on incidence of TB. Some areas of GM are considered to have high incidence. Isolated cases of neonates who died from disseminated BCG vaccination or TB infection after exposure to an anti-TNF medicine in utero were reported to MHRA. they were probably not known to be immunosuppressed at the time of vaccination. (25) The BCG vaccine may easily be deferred to be given later in life. (13)
- Rotavirus - all infants. Rotavirus is the most common cause of gastroenteritis in infants in the UK. (26) The rotavirus course of vaccination must be completed by 24 weeks of age due to risk of intussusception. (26) Although there is limited evidence of safety and efficacy in infants with immunosuppression, vaccination of infant exposed in utero may be considered following careful consideration of the risks and benefits and following specialist consultation.

For advice on other live vaccinations following exposure to biologics in breastmilk, healthcare professionals should contact the relevant specialist for advice.

If there is any doubt as to whether an infant due to receive a live attenuated vaccine may be immunosuppressed due to the mother's therapy, including exposure through breast-feeding, specialist advice should be sought. (27)

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.

19. Vaccinations

19.1. Routine vaccinations

Where possible, vaccination requirements should be reviewed and brought up to date prior to initiation of biologic therapy, with reference to Department of Health Guidance. During biologic therapy, patients should receive (inactivated) influenza vaccine annually and pneumococcal vaccine once only. For vaccination of infants see [section 18.4](#).

19.2. Live vaccines

The administration of live vaccines is contraindicated in patients on biologic agents and cautioned in patients on JAK inhibitors. It is safe to administer a live vaccine 4 weeks prior to commencing biologic or tofacitinib therapy, when necessary. There is no contraindication for the administration of live vaccines to relatives or friends of patients on biologic or immunosuppressant drugs.

When a live vaccine is required by a patient on a high cost drug, stopping treatment (following careful assessment of the risks and benefits) may enable a necessary vaccination to be administered. The decision to vaccinate should be guided by the drug half-life (see table 3 in [section 17](#)). For further relevant summaries of products characteristics, www.medicines.org.uk

- the Green Book, <https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book> (27)
- Specialist advice

The table below shows all live vaccines available in the UK.

Table 6. Live vaccines available in the UK

Live vaccine	Brand name(s)
Tuberculosis - BCG	Bacillus Calmette-Guerin Vaccine
Influenza (nasal)	Brand can change yearly in the UK
Measles, mumps and rubella combined vaccine (MMR)	MMRvaxPRO®, Priorix®
Rotavirus (Live oral vaccine)	Rotarix®
Typhoid (Live oral vaccine)	Vivotif®
Varicella-Zoster vaccine	Varilrix®, Varivax®, Zostavax®
Yellow fever vaccine	Stamaril®

19.3. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on high-cost therapies, though they may elicit a lower response than in immunocompetent individuals.

Non-live vaccines should be given 2-4 weeks before starting immunosuppressant therapy, as response after starting treatment can be poor.

For information on specific vaccines please refer to the appropriate Summary of Product Characteristics (www.medicines.org.uk) or the [Green Book: Immunisation against infectious disease](#). (27)

For information on COVID-19 vaccines please refer to the [Green Book: Immunisation against infectious disease Chapter 14a](#).

Shingrix® a non-live vaccine for varicella zoster virus (VZV) is now available in the UK. From 2021, individuals who are eligible for shingles vaccine (adults aged 70-79 years), but who are contra-indicated to the receipt of the live vaccine should be offered Shingrix® instead. Adults should receive two doses of Shingrix® a minimum of 2 months apart. For more information please refer to the [Green Book: Immunisation against infectious disease Chapter 28a](#) (27)

20. Checklist for patient screening on selection for high cost drugs

Screening investigations requested in clinic			
	Y/N	Initial	Results/Details
FBC/U&E/LFT/ESR/CRP			
ANA (If positive also order ENA/dsDNA/C3/C4)			
HIV, HBV (surface antigen, core antibody)*, HCV (antibody test) If positive result please refer to hepatology/GUM/ID as relevant <small>*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</small>			
Varicella zoster IgG (If negative inform GP and patient)			
TB screening (g-IFN testing) If positive refer to respiratory			
Chest X-ray (within the last 6 months) (± pulmonary function tests/HRCT thorax) CXR checked by/date			
Additional investigations for rheumatoid arthritis	Ensure RF/anti-CCP status Don't repeat if previously positive result.		
Additional investigations for rituximab	Serum immunoglobulins (document low level & seek advice if appropriate: monitor if low especially in older patients) (+/- B cells)		
Additional monitoring: Tocilizumab/Sarilumab/JAKi	Fasting lipids (if abnormal treat according to local guidelines)		
Screening questions asked in clinic			
	Y/N	Initial	Details
Previous TB/TB contact (details)			
Travel abroad since last review (i.e., TB/viral hepatitis high risk countries) Which country/Dates			
History of heart failure (NYHA class III or IV) (details)			
History of recurrent infection (details)			
History of interstitial lung disease (details such as extent of ILD)			
History of cancer/malignancy (Type/Date when occurred/Date of all clear)			
Date of last mammogram (50yr +) (encourage patient to visit GP if >3 years)			
Date of last smear (25yr +) (encourage patient to visit GP if >3 years)			
History of allergy/infusion reaction to any agent (to what/type of reaction)			
History of cardiovascular risk factors			
History of thrombotic event (e.g. DVT/PE)			
Any live vaccinations in the last 4 weeks			
History of demyelinating disease (details)			
History of diverticular disease (details)			
Concurrent immune disease (e.g., uveitis, IBD, psoriasis)			
Education			
Pregnancy/breastfeeding advice given			
Vaccination advice given			
Patient counselled and educated			
Patient consent to be approached for research			

21. Specific monitoring considerations

See screening questionnaire ([section 20](#)) for full details of baseline monitoring that should be performed in all patients considered for high cost drugs.

Ongoing monitoring in line with BSR guidance is recommended for all patients, e.g., FBC, creatinine/calculated GFR, ALT/AST and albumin every 3-6 months. (10). Additional monitoring is recommended for some biologics and for the JAK inhibitors, as described below. Monitoring for other adverse events not mentioned in the tables below e.g. skin malignancy, should be done as recommended by the manufacturer, during patient review in consideration to treatment continuation or change.

21.1 Tocilizumab and sarilumab

FBC (monitoring of absolute neutrophil count [ANC] and platelets) (4; 10)		
Recommended monitoring	<ul style="list-style-type: none"> Check FBC 4-8 weekly for the 1st 6 months then every 12 weeks thereafter. Timing of these tests should ideally be: <ul style="list-style-type: none"> IV tocilizumab: before the next scheduled infusion SC tocilizumab 3 days before every fourth injection SC sarilumab 3 days before every fourth injection 	
Recommended actions	ANC (laboratory value: cells x 10 ⁹ /L)	
	Initiation is not recommended in patients with ANC <2 x 10 ⁹ /L	
	>1	Maintain dose
	0.5 to 1	Interrupt dosing. When ANC >1, resume as below.
	<0.5	Discontinue treatment
	Platelets (laboratory value: cells x 10 ³ /microlitre)	
	50 to 100	Interrupt dosing. When platelets >100, resume as below
	<50	Discontinue treatment
Resuming after interruption		
<ul style="list-style-type: none"> Tocilizumab IV: resume at 4 mg/kg. Increase to 8 mg/kg as clinically appropriate. Tocilizumab SC: resume with every other week dosing. Increase to weekly when appropriate Sarilumab: resume at 150 mg every 2 weeks and increase to 200 mg every 2 weeks as clinically appropriate 		
LFTs (monitoring of transaminases: ALT & AST) (4; 10)		
Recommended monitoring	<ul style="list-style-type: none"> Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported. When clinically indicated, other LFTs including bilirubin should be considered. Check LFTs 4-8 weekly for the 1st 6 months then every 12 weeks thereafter. Timing of these tests should ideally be <ul style="list-style-type: none"> IV tocilizumab: the week before the next scheduled infusion SC tocilizumab 3 days before every fourth injection SC sarilumab 3 days before every fourth injection 	
Recommended actions	>1 to 3 x upper limit of normal (ULN)	Dose-modify concomitant DMARDs, if appropriate. For persistent increases in this range reduce dose of <u>tocilizumab</u> as below, or interrupt until ALT/AST have normalised. No dose reduction is recommended for <u>sarilumab</u> <ul style="list-style-type: none"> IV tocilizumab: reduce dose to 4 mg/kg. Restart at 4 mg/kg or 8 mg/kg, as clinically appropriate SC tocilizumab: reduce dose to every other week. Restart with weekly or every other week injection, as clinically appropriate.
	>3 to 5 x ULN	Interrupt treatment until <3 x ULN, then: <ul style="list-style-type: none"> Tocilizumab: Follow recommendations above for restarting treatment after elevations >1 to 3 x ULN Sarilumab: Resume at 150 mg every 2 weeks and increase to 200 mg every 2 weeks as clinically appropriate
	>5 x ULN	Discontinue treatment
Lipids (4; 10)		
Recommended monitoring and actions	Tocilizumab & sarilumab <ul style="list-style-type: none"> Fasting lipid profile should be assessed at baseline and repeated at 3 months Studies have suggested that any initial rise in lipid levels tends to stabilise within 3 months, and BSR currently recommend that the repeat lipid profile should be performed at 3 months. (10) Any further monitoring should be in line with local practice and guided by presence of other risk factors. Increase in lipid profile should be treated as per local policy 	

21.2 Rituximab

Serum immunoglobulins (4; 10)

Recommended monitoring	<ul style="list-style-type: none"> Check immunoglobulins at baseline (IgA, IgG, and IgM). Low level of immunoglobulins, especially IgG, is associated with a higher risk of neutropenia and infection in patients receiving rituximab Check serum immunoglobulins prior to each cycle of rituximab.
Recommended actions	<ul style="list-style-type: none"> Risk of infection increases as serum IgG falls below normal. Consider reduced rituximab dose (e.g., 2 x 500 mg infusions) in this situation There is no evidence to establish an absolute threshold for total immunoglobulin, IgG or IgM where rituximab should be withheld.

21.3 Tofacitinib

Dose adjustments are required in hepatic and renal impairment. See below and [SPCs](#) for further information. Monitoring of tofacitinib differs from that of other JAK inhibitors and therefore is tabulated separately.

[MHRA: Janus kinase \(JAK\) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality](#) (2023). It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current, or past long-time smoking and other factors for cardiovascular disease or malignancy.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (4)

Recommended monitoring	<ul style="list-style-type: none"> Check FBC at baseline, 4-8 weeks after initiating treatment, and 3-monthly thereafter 	
Recommended actions	ALC (laboratory value: cells x 10 ⁹ /L)	
	Initiation is not recommended in patients with ALC <0.75	
	ALC >0.75	Maintain dose
	ALC 0.5-0.75	<ul style="list-style-type: none"> If ≥2 sequential values in this range, <ul style="list-style-type: none"> tofacitinib 5 mg BD or 11 mg OD: interrupt dosing When ALC >0.75, treatment should be resumed as clinically appropriate.
	ALC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	ANC (laboratory value: cells x 10 ⁹ /L)	
	Initiation is not recommended in patients with ANC <1	
	ANC >1	Maintain treatment
	ANC 0.5-1.0	<ul style="list-style-type: none"> If ≥2 sequential values in this range, <ul style="list-style-type: none"> tofacitinib 5 mg BD or 11 mg OD: interrupt dosing When ANC >1, treatment should be resumed as clinically appropriate.
	ANC <0.5	Confirm with repeat testing within 7 days. If confirmed, discontinue
	Haemoglobin (laboratory value: g/dL)	
	Initiation is not recommended in patients with haemoglobin <9 g/dL	
	Decrease ≤2, and absolute value ≥9	Maintain dose
	Decrease >2 or absolute value <8	Confirm with repeat testing. Interrupt dosing until haemoglobin values have normalised.

Hepatic transaminases (ALT & AST)

Recommended monitoring	<ul style="list-style-type: none"> Check hepatic transaminases at baseline and thereafter according to routine management
Recommended actions	<ul style="list-style-type: none"> Temporarily interrupt treatment if drug-induced liver injury is suspected

Lipid parameters

Recommended monitoring	<ul style="list-style-type: none"> Lipid parameters should be assessed at baseline and repeated after 8 weeks. Maximum effects on lipid parameters are normally seen within 6 weeks. Treat as per local practice guidelines
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Renal impairment

Recommended actions	<ul style="list-style-type: none"> Creatine clearance <30ml/min dose should be reduced to 5mg once daily <p style="text-align: right;"><i>...continued over next page</i></p>
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Age considerations

Recommended actions

- Only use in patients 65 years of age and older if no suitable treatment alternatives are available.
- No dose adjustment is required in patients 65 years of age and older.
- There are limited data in patients aged 75 years and older.

Other safety considerations (MACE, VTE, malignancy)

Recommended actions and monitoring

- Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.
- For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is $\geq 2 \times$ ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.
- Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.
- Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

21.4 Baricitinib, filgotinib, upadacitinib

Monitoring of tofacitinib differs from that of other JAK inhibitors and therefore is tabulated separately.

[MHRA: Janus kinase \(JAK\) inhibitors: new measures to reduce risks of major cardiovascular events, malignancy, venous thromboembolism, serious infections, and increased mortality \(2023\)](#). It is advised to avoid prescribing JAK inhibitors unless there are no suitable alternatives in patients with the following risk factors: age 65 or older, current, or past long-time smoking and other factors for cardiovascular disease or malignancy.

FBC (monitoring of absolute lymphocyte count [ALC], absolute neutrophil count [ANC], and haemoglobin) (4)

Recommended monitoring

- Check FBC at baseline and then no later than 12 weeks after initiation of treatment

Recommended actions

ALC (laboratory value: 10^9 cells/L)

ALC > 0.5 Continue treatment

ALC < 0.5 Interrupt treatment. Restart once ALC > 0.5.

ANC (laboratory value: 10^9 cells/L)

ANC > 1.0 Continue treatment

ANC < 1.0 Interrupt treatment. Restart once ANC > 1.0.

Haemoglobin (laboratory value: g/dL)

Hb > 8 Continue treatment

HB < 8 Interrupt treatment. Restart once Hb > 8

Hepatic transaminases

Recommended monitoring

- Check hepatic transaminases at baseline and thereafter according to routine management
Note: In the filgotinib SmPC there is no requirement for monitoring of hepatic transaminases.

Recommended actions

- Temporarily interrupt treatment if drug-induced liver injury is suspected

Lipid parameters

Recommended monitoring

- Lipid parameters should be assessed at baseline and repeated after 12 weeks.

Recommended actions

- Treat any lipid abnormalities in line with local practice.

Renal impairment*...continued over next page*

Recommended actions

Baricitinib

- The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Baricitinib is not recommended for use in patients with creatinine clearance < 30 mL/min

Recommended actions

Filgotinib

- A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) and is therefore not recommended for use in these patients.

Recommended actions

Upadacitinib

- No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment. Upadacitinib 15 mg once daily should be used with caution in patients with severe renal impairment.

Age considerations	
Recommended actions Baricitinib	<ul style="list-style-type: none"> • Only use in patients 65 years of age and older if no suitable alternative. The recommended dose is 2mg once daily. • Clinical experience in patients aged ≥ 75 years is very limited.
Recommended actions Filgotinib	<ul style="list-style-type: none"> • Only use in patients aged 65 years and older if no suitable alternative. The recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.
Recommended actions Upadacitinib	<ul style="list-style-type: none"> • Only use in patients aged 65 years and older if no suitable alternative (no dose adjustment). • There are limited data in patients 75 years of age and older.
Other safety considerations (MACE, VTE, malignancy)	
Recommended monitoring	<ul style="list-style-type: none"> • Patients should be re-evaluated periodically during baricitinib treatment to assess for changes in VTE risk. • Promptly evaluate patients with signs and symptoms of VTE and discontinue baricitinib in patients with suspected VTE, regardless of dose or indication. • Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.
Recommended actions Baricitinib	<ul style="list-style-type: none"> • A dose of 2 mg once daily is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections.
Recommended actions Filgotinib	<ul style="list-style-type: none"> • In adults at increased risk of VTE, MACE and malignancy, and those aged 65 and older, the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.
Recommended actions Upadacitinib	<ul style="list-style-type: none"> • No dose adjustment.

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