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Clinical Guideline

Rheumatoid Arthritis
Drug Treatment Pathway

Guideline Summary
This clinical guideline outlines the biologic treatment pathway for adult patients with rheumatoid arthritis.

South East London Area Prescribing Committee: A partnership between NHS organisations in South East London; Bexley/Bromley/Greenwich/Lambeth/Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTfT/KCH/SLAM & Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust.
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Author	**South East London Rheumatology Steering Group**: Acute Trusts: **Guys and St Thomas' NHS Foundation Trust** Principal Pharmacist Immunotherapy (Rheumatology, Dermatology, Allergy) and Clinical Commissioning Highly Specialist Pharmacist Rheumatology Consultant Rheumatologist and Clinical Lead Rheumatology Consultant Rheumatologist Consultant Rheumatologist Advanced Nurse Specialist, Rheumatology **Kings College Hospital NHS Foundation Trust** Consultant Rheumatologist (Chair) Clinical pharmacy team leader – Post-acute and Planned Medicine Consult Rheumatologist and Clinical Lead Rheumatology **Lewisham and Greenwich NHS Trust** Consultant Rheumatologist Clinical Nurse Specialist, Rheumatology Lead Pharmacist Long term Conditions **Clinical Commissioning Groups:** NHS Lambeth CCG (Lead CCG), NHS Southwark CCG, NHS Bexley CCG, NHS Bromley CCG NHS Greenwich CCG, NHS Lewisham CCG
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Change History			
Date	Change details, since approval		Approved by
3.11.16	5.1	Update of pre-biologic therapy definition	
3.11.16	7.	Update of vaccination requirement	
3.11.16	9.	Addition of free of charge schemes	
3.11.16	13.	Addition of biologic choice in women planning therapy	
3.11.16	14-16	Revision of pathways	
3.11.16	17.0	Addition of treatment options following multiple biologic failures	
3.11.16	18.0	Update of key performance indicators for annual audit	
09.12.16	14	Golimumab 50mg twice monthly dosing statement added to notes box	
27.01.17	7 – added info on administration of vaccinations by early outpatient biologic initiation service		
27.01.17	11 – added info on administration of first dose biologic via OP clinic and VAT charge to commissioners		
08.03.17	5 & 8 – detail added re: STRAP trial		
October 2017	Addition of baricitinib and tofacitinib following positive NICE approval		
March 2018	Addition of subcutaneous methotrexate billing information, pre-biologic infection screen addition of quantiferon		
March 2018	Addition of sarilumab following positive NICE approval and update of NICE guidelines in references		MPRG

Review History		
Date	Review details	Approved by
March 2018	Updated in line with latest NICE TAGs (see change history)	

Contents

1. Scope

This treatment pathway applies to adult patients with a diagnosis of highly active rheumatoid arthritis (DAS 28>5.1) who are approaching treatment with biologic therapy.

2. Rationale

This treatment pathway provides an evidence based approach for the treatment of rheumatoid arthritis whilst maximising cost effectiveness and clinical outcome.

3. Principles

This treatment guideline is based on current available national guidance (National Institute for Health and Care Excellence, NICE), locally approved guidance and is subject to frequent change as guidance is updated and costs change.

4. Definitions

EULAR Response Criteria:

DAS28 Improvement →	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
Present DAS 28 ↓			
≤ 3.2	good response	moderate response	no response
> 3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

Primary failure – patient does not respond after 6 months treatment (3 months for certolizumab pegol) – refer to section 14

Secondary failure – patient initially achieves a good or moderate response after 6 months but this is not sustained resulting in failure to maintain a reduction of 1.2 points or more – refer to section 16

5. Pre-biologic therapy [disease modifying anti-rheumatic drugs (DMARDs)]

5.1. Pre-biologic therapy

Persistent Active Rheumatoid Arthritis
(DAS 28>5.1)
+
Failure of intensive therapy with a combination of conventional DMARD therapy

Strategies for maximising the use of DMARDs prior to biologic therapy:

- Adjusting folic acid dose/frequency/formulation to improve tolerance to oral methotrexate (e.g. folic acid liquid 1mg daily except day of methotrexate)
- Subcutaneous methotrexate where clinically appropriate (e.g. gastrointestinal adverse effects with oral methotrexate or poor compliance) When used in this situation, billable to CCGs for approved indications in line with the CCG high cost drugs policy and CCG commissioned drug list. Whilst the majority of dispensing will be via homecare, commissioners have agreed that there may be exceptional circumstances where homecare may not be possible (e.g. due to patient circumstances or to cover initiation doses) and these can be billed.

- Maximum intensification of combination therapy, for example:
  - Has maximum tolerable dosage been achieved?
  - Has triple DMARD therapy been considered (unless contraindicated)?

5.2. In combination with biologics

Where patients are intolerant of methotrexate or methotrexate is considered inappropriate, other DMARDs may be used in combination with biologics although this combination may be considered 'off-label'.

6. Pre-biologic Infection screen

- TB (T spot or quantiferon and chest x-ray)
- Viral serology: hepatitis B, C and HIV as clinically appropriate

7. Vaccinations **(click for Department of Health Green Book)**

Patients should be counselled on the need to avoid live vaccines and the implication that may have for travelling.

Patients aged 70 years and over are now routinely offered vaccination against varicella zoster virus in primary care. This is a live vaccination and patients should not be given the vaccine if they are receiving biologic treatments. For patients aged over 60 and not receiving biologic treatment, the Consultant Rheumatologist may consider recommending the vaccine after careful assessment of the degree of current immunosuppression from DMARDs and glucocorticoids. To avoid inadvertent administration of this live vaccine, on receipt of clinic letters, GPs should update practice records to indicate which patients are currently receiving biologic treatment.

Patients should receive annual influenza vaccine and pandemic influenza vaccine when recommended and pneumococcal vaccination prior to biologic therapy. This can be prescribed and administered in the community or by the hospital as part of an outpatient biologic initiation service. GP's must be informed if the hospital administer to outpatient.

8. Recruitment into clinical trials

Where possible, patients should be invited to participate in clinical trials being undertaken within rheumatology departments. Where a clinical trial does not meet the requirements of the pathway approval should be obtained from commissioners prior to initiation.

STRAP (Stratification of Biologic Therapies for RA by Pathobiology) is a Medical Research Council funded multi centre phase III randomised, open-label, biopsy-driven stratification trial in DMARD inadequate responders, fulfilling NICE criteria to commence biological therapy. It aims to identify treatment response predictors which will allow the stratification of patients to the biological therapy they are most likely to respond to.

9. Free of Charge Schemes

New biologic and non-biologic DMARDS are often licensed and made commercially available many months before NICE are due to issue their NICE Technology Appraisal Guidance. Where this situation exists, individual rheumatology departments may enter discussions with the pharmaceutical company to determine if a 'free of charge' (FOC) early access scheme is feasible.

When a FOC is proposed it must satisfy the following criteria:

- Fund the treatment at zero cost to the NHS up to and for 90 days after the positive NICE Technology Appraisal Guidance is issued and formally commissioned
- Continue to fund treatment in the event of a negative NICE Technology Appraisal Guidance until
    - 90 days after a future positive NICE Technology Appraisal Guidance
    - Until the rheumatologist considers it no longer clinically appropriate to continue the drug
- All schemes require sign off in each NHS Trust and this usually requires the Chief Pharmacist, the Pharmacy Procurement Lead and Director of Finance to authorise the scheme.

10. Extended interval dosing ('off-label' indication) and biologic withdrawal in remission

After discussion with the patient a Consultant may decide to extend the dosage interval or withdraw biologic therapy completely as appropriate for the clinical situation. This may require the use of ultrasound to confirm if patient is in remission. If patients flare following extension in dose interval or withdrawal; re-initiation of the previous biologic at the same dosage regimen is acceptable but consider using an alternative agent due to immunogenicity. Whilst a patient maintains remission or low disease activity on an extended dose interval, the Trust can recover a share of the savings from the commissioner. This is subject to local discussion and contractual agreement.

11. Method of medication supply

Subject to local arrangements patients may be offered a choice of method of supply. This may include a traditional homecare service or enhanced outpatient pharmacy service via outsourced outpatient pharmacies on main hospital sites. Where there is agreement with pharmaceutical companies, unbundling of homecare and direct procurement via outsourced pharmacies may result in a reduction in the drug acquisition cost. This may further influence the biologic choice at local Trust level.

In order to reduce the time to biologic initiation, the first biologic doses (2 – 4 weeks supply) may be given in clinic as part of an outpatient biologic initiation service. This provides sufficient supply, improved patient training and assessment in clinic prior to initiation on homecare. As the first dose(s) are administered in the outpatient clinic, the cost will incur VAT and this will be passed onto commissioners.

12. Biologic choice in patients unable to take methotrexate (MTX, oral and subcutaneous)

The majority of patients commencing biologics are on concurrent methotrexate. However, for the minority who are not, the chances of a meaningful response to therapy are lower. Between 10 – 37% of patients discontinue methotrexate due to adverse effects[13] and data from the British Society of Rheumatology Biologics Register indicate that approximately a third of patients take biological disease modifying antirheumatic drugs as monotherapy[14].

NICE TA 247 (February 2012) recommended tocilizumab in combination with methotrexate as a first line biologic after DMARD failure or as a second line biologic in patients unable to have rituximab.

The ADACTA study[15] published in May 2013, evaluated the efficacy, safety and superiority of intravenous tocilizumab monotherapy (n=163) compared to subcutaneous adalimumab monotherapy (n=162) in adult patients with rheumatoid arthritis. At week 24 the mean change from baseline in DAS28 was significantly greater in the tocilizumab group (-3.3) than in the adalimumab group (-1.8). Importantly, whilst the absolute reduction in DAS may seem small, it is notable that in the tocilizumab group, approximately 40% of patients achieved remission, compared to just below 10% in

the adalimumab arm. This represents a highly clinical relevant difference. The rate of adverse events in the tocilizumab group (12%) was higher than in the adalimumab group (10%).

The marketing authorisation for tocilizumab includes the option of monotherapy and the Scottish Medicines Consortium has accepted tocilizumab monotherapy for patients with intolerance to methotrexate or where methotrexate is considered inappropriate.

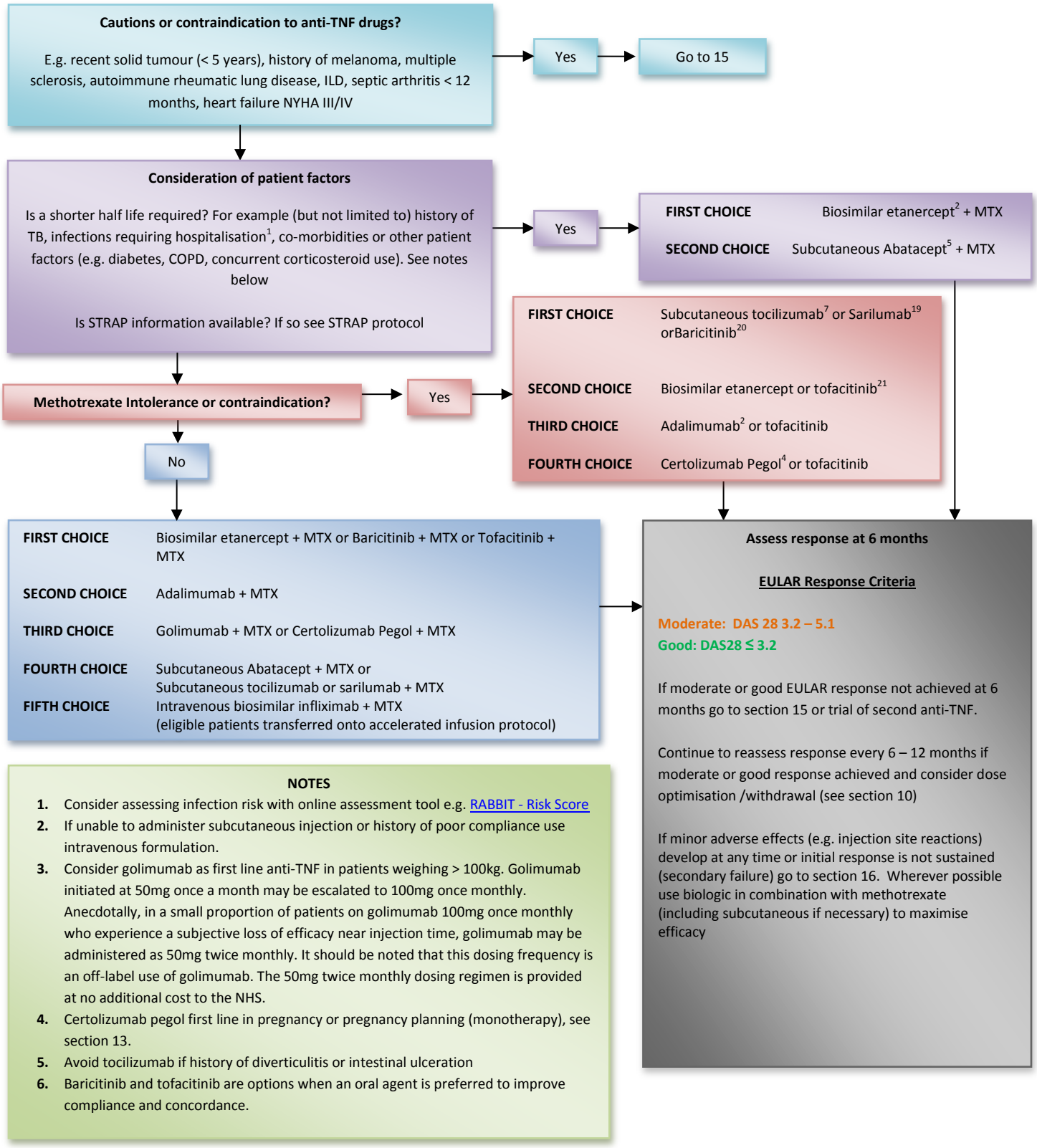
Nonetheless, whilst tocilizumab is an important option, it remains the case that it is still preferable to use all biologics alongside methotrexate, where superior efficacy remains. Tocilizumab monotherapy is an option only for the minority of patients unable to take methotrexate. In addition, it is envisaged that the usage will primarily be with the subcutaneous preparation as this is more convenient for patients and reduces the administration cost burden. Intravenous administration will be used only where there are exceptional circumstances (e.g. serious concerns about capability or compliance).

On this basis this pathway supports the use of tocilizumab (subcutaneous or intravenous) for the treatment of rheumatoid arthritis in patients that are unable to take methotrexate due to intolerance or contraindications.

13. Biologic choice in women planning pregnancy

Certolizumab pegol is compatible with all three trimester of pregnancy and has reduced placental transfer when compared with other TNF inhibitors. For these reasons it is the biologic of choice before, during and after pregnancy (whilst breast feeding). Patients may require to be switched from their current biologic to certolizumab pegol in advance of conception. This should not count as a routine biologic switch. For further recommendations on biologic or conventional DMARD choice in pregnancy or breast feeding, refer to the BSR/BHPR guideline:
http://www.rheumatology.org.uk/resources/guidelines/default.aspx

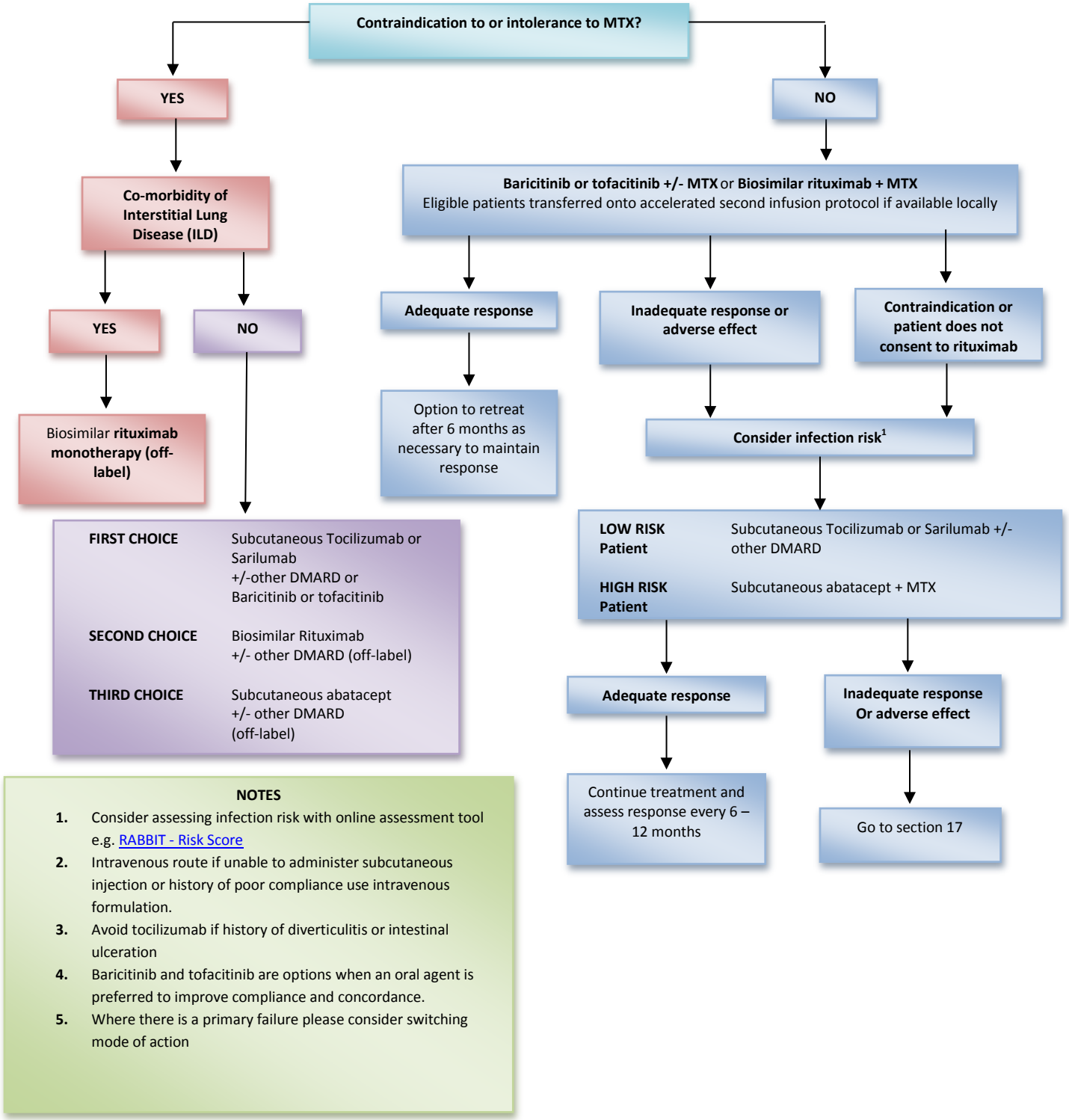
14. Initiation of first biologic



NOTES

1. Consider assessing infection risk with online assessment tool e.g. RABBIT - Risk Score
2. If unable to administer subcutaneous injection or history of poor compliance use intravenous formulation.
3. Consider golimumab as first line anti-TNF in patients weighing > 100kg. Golimumab initiated at 50mg once a month may be escalated to 100mg once monthly. Anecdotally, in a small proportion of patients on golimumab 100mg once monthly who experience a subjective loss of efficacy near injection time, golimumab may be administered as 50mg twice monthly. It should be noted that this dosing frequency is an off-label use of golimumab. The 50mg twice monthly dosing regimen is provided at no additional cost to the NHS.
4. Certolizumab pegol first line in pregnancy or pregnancy planning (monotherapy), see section 13.
5. Avoid tocilizumab if history of diverticulitis or intestinal ulceration
6. Baricitinib and tofacitinib are options when an oral agent is preferred to improve compliance and concordance.

15. Initiation of first biologic (anti-TNF contraindicated) OR primary failure* with first anti-TNF[5,7,19,20,21] (*defined as no patient response after 6 months treatment (3 months for certolizumab pegol) see section 4)

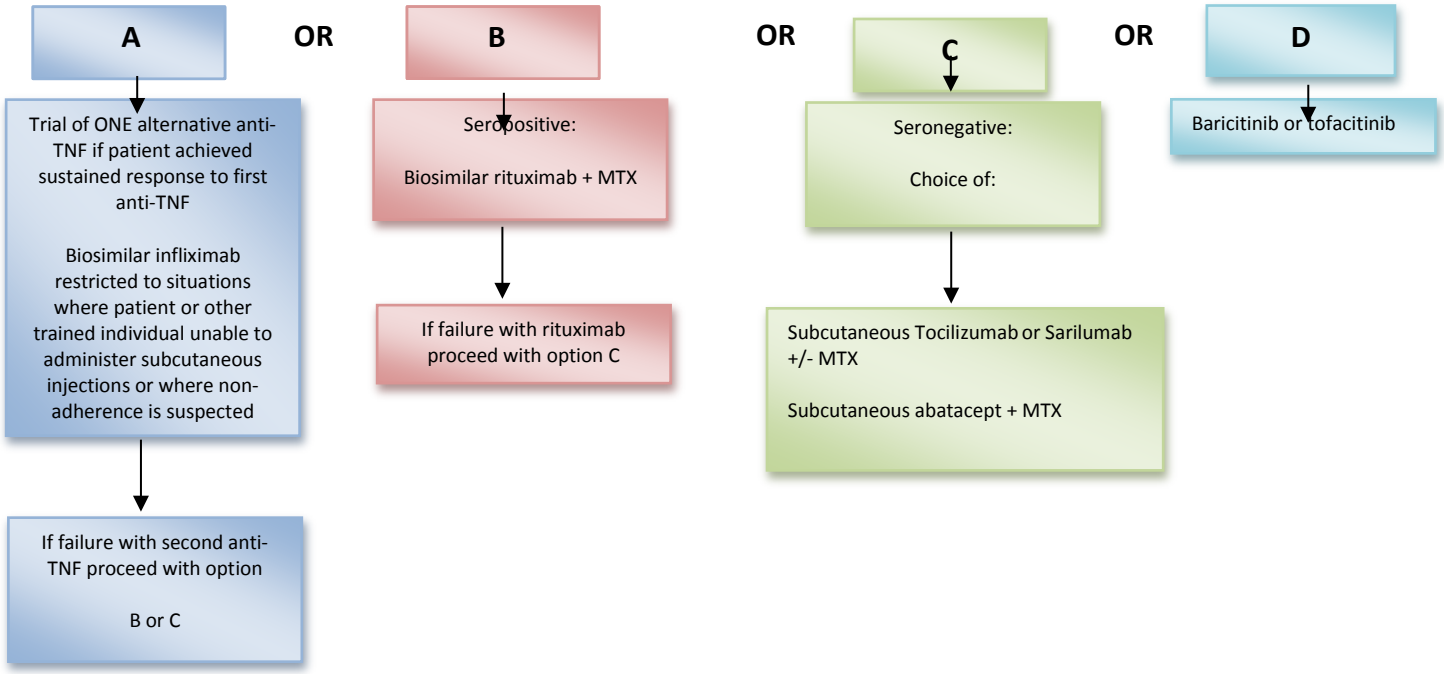


NOTES

1. Consider assessing infection risk with online assessment tool e.g. RABBIT - Risk Score
2. Intravenous route if unable to administer subcutaneous injection or history of poor compliance use intravenous formulation.
3. Avoid tocilizumab if history of diverticulitis or intestinal ulceration
4. Baricitinib and tofacitinib are options when an oral agent is preferred to improve compliance and concordance.
5. Where there is a primary failure please consider switching mode of action

16. Secondary Failure or minor adverse effects (e.g. injection site reactions) with first anti-TNF

Options for consideration:



DAS 28 measured at 12 - 24 weeks. Continue if adequate response and reassess every 24 - 52 weeks. If possible use biologic in combination with methotrexate (oral or subcutaneous) to maximise efficacy. Where methotrexate cannot be used, alternative DMARD(s) should be used.

17. Treatment options following multiple biologic treatment failures including where biologics are contraindicated, not tolerated or in cases of hypersensitivity.

- Consultant rheumatologist to determine if active synovitis present (if in any doubt ultrasound should be considered)
- Consider novel agents if accessible via free of charge patient access schemes e.g. janus kinase inhibitors
- Revert back to biologic that delivered best clinical outcomes or use alternative biologic in same mode of action class with lowest acquisition costs
    - Decision should be made in a Multidisciplinary Team (MDT) discussion in the local rheumatology department
    - Clinical outcomes and baseline scores must be reported to the CCG using a Category B form
    - Include current corticosteroid dose or use of methylprednisolone in previous 6 – 12 months
    - Measure disease scores e.g HAQ, EQ5D, DAS
- Category B forms are reviewed at South East London (SEL) Rheumatology Pathway Development Group meetings

18. Monitoring adherence with the guideline

Adherence to this pathway will be reviewed using the SEL Rheumatology Pathways, Outcomes and Monitoring Framework which includes Key Performance Indicators agreed by South East London Area Prescribing Committee. See http://www.lambethccg.nhs.uk for further details. The Rheumatology and Pharmacy Departments may undertake separate clinical audits as part of their annual clinical audit plan.

19. Supporting documents (see relevant local guidelines)

- Protocol for administration and reducing infusion times of infliximab in adult rheumatology patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.
- Protocol for the use of self-administered sub-cutaneous methotrexate injection (Metoject) in adult patients with rheumatoid arthritis.
- Protocol for the use of rituximab for the treatment of autoimmune rheumatic diseases (including rheumatoid arthritis) in adults.

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21. NICE Technology appraisal guidance TA 480 Tofacitinib for moderate to severe rheumatoid arthritis. October 2017

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SEL Medicines and Pathways Review Group (MPRG): April 2018