Executive Summary

The current version of the GMMMG's High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults was published in June 2019 and review suggested for December 2019 in light of upcoming NICE recommendations. However, the review was been delayed until autumn 2021 due to Covid-19.

Key Points

The main changes include:

- Updates to incorporate new products, marketing authorisations updates and NICE TAs published since previous version of the pathway.
- Addition of the recent Drug Safety Update for tofacitinib.
- Incorporation of the off-label escalation of infliximab (already established as clinical practice in Greater Manchester trusts). Rationale paper available on demand.
- Statement on interchangeability of two biosimilar infliximab products: Inflectra® and Remsima® (identical formulation of biosimilar produced by single manufacturer, Celltrion, but marketed under different brand names).

The pathways have been drafted to reflect the group's preference that local multidisciplinary team (MDT) decision replace need for individual funding request (IFR) in patients receiving more than four sequential high cost drugs.

Views on the above, and in particular on the MDT's role, are encouraged from the representatives of all healthcare sectors in Greater Manchester and the public. The pharmaceutical industry is invited to comment on factual inaccuracies only.

High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults

November 2021

Version 4.2 FINAL DRAFT

This version supersedes version 3.0

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Authors:

Dr Scott Levison[1], Vanessa Reid[2], Adele MacKellar[3], Dr Karen Kemp[4], Wai-Ling Chau[5], Rachel Daughney[6], Bethan Faulkner[7], Mohsin Gangi[8], Suzanne Tattersall[9], Jo Taylor[10], Marianne Sian Ellis[11], Anna Pracz[12]

[1]Consultant Gastroenterologist, Manchester Royal Infirmary, MFT
[2]Lead Specialist Clinical Pharmacist, Manchester Royal Infirmary, MFT
[3]Specialist Clinical Pharmacist, Wythenshawe hospital, MFT
[4]Nurse Consultant Inflammatory Bowel Disease, Manchester Royal Infirmary, MFT
[5]Specialist Pharmacist, MFT
[6]Gastroenterology specialist pharmacist, Stepping Hill Hospital, Stockport FT
[7]Specialist Pharmacist Homecare and High Cost Drugs, Pennine Acute
[8]Consultant Gastroenterologist, Stepping Hill Hospital, Stockport FT
[9]Lead Nurse IBD, Royal Bolton Hospital, Bolton FT
[10]Lead Inflammatory Bowel Disease Clinical Nurse Specialist , Fairfield General Hospital, PAT
[11]Specialist Pharmacist - High Cost Drugs and Homecare , Pharmacy, Fairfield General Hospital and Rochdale Infirmary
[12]Senior Medicines Optimisation Pharmacist, Greater Manchester Joint Commissioning Team

DOCUMENT CONTROL

Revision history

The latest and master version of this document is held on the GMMMG website.

REVISION DATE	ACTIONED BY	SUMMARY OF CHANGES	VERSION
September 2017	IBD working group	Added ustekinumab following publication of NICE TA456	1.1
October 2017	IBD working group	Changes to special situations	1.2
November 2017	IBD working group	Changes made following consultation	1.3
November 2017	Sarah Jacobs	Final changes to vaccinations & special situations. Amendments to flow charts.	1.4
March 2019	Anna Pracz	Added tofacitinib as per NICE TA547. Minor amendments to reflect addition of non-biologic high cost drug to the guideline. Changes to the special considerations & vaccinations section.	2.1
April 2019	Anna Pracz	Amended as per steering group's comments	2.2
May 2019	Anna Pracz	Amended as per final comments on draft 1.6 from the steering group. Incorporation of NICE NG129, NICE NG130 and MHRA's tofacitinib safety alert with changes to the document as relevant. Optimal infliximab trough levels on pathway C amended following results of PANTS study.	2.3
June 2019	Anna Pracz	Final draft presented to HCDOG and approved	3.0
June 2020	RDTC	Updated to reflect most recent clinical guidance. Added NICE TA633 for ustekinumab in UC and subcutaneous infliximab formulation. Flowcharts updated	4.0
October 2021	Anna Pracz	Updated to reflect most recent clinical guidance. Added dose optimisation section including off-label escalation of infliximab.	4.1.
November 2021	Anna Pracz	Updated to include DSU for tofacitinib and clarify changes to IFR approval route, following MGSG	4.2

Approvals

This document must be approved by the following before distribution:

NAME	DATE OF ISSUE	VERSION
IBD working group	12.10.21	4.1
MGSG	25.10.21	4.2
GMMMG		

Final version available on GMMMG website **http://gmmmg.nhs.uk/**

Contents

High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults

1. Background

These pathways are to be used as guidelines in the initiation and maintenance of high cost drugs in the management of inflammatory bowel disease (IBD) in adults, including ulcerative colitis and Crohn's disease. These pathways have been written using up to date published research and evidenced based medicine. This originated as a clinical project implemented by MAHSC and is a joint project between the gastroenterology departments of the Greater Manchester hospital trusts.

Currently the pathways include biologic agents: tumour necrosis factor inhibitors (anti-TNFs; infliximab, adalimumab and golimumab), an integrin inhibitor (vedolizumab), and an interleukin inhibitor (ustekinumab). More recently, a novel therapy with a non-biologic high cost drug, a Janus kinase inhibitor (JAK-inhibitor; tofacitinib), has been made available as a treatment option for patients with ulcerative colitis.

2. NICE guidance

The links to relevant NICE guidance are listed below. Any new high cost drugs that are approved by NICE between GMMMG IBD pathway iterations will be considered for placement in this pathway. The use of any new NICE approved high cost drugs will be allowed prior to inclusion in the pathway, provided that the total number of drugs allowed in pathway has not been exceeded. Those drugs should be used in accordance with the relevant NICE TA.

The NICE recommendations also apply to biosimilar drugs, where marketing authorisations allow use of the biosimilar for the indication specified in the relevant NICE TA.

2.1. Crohn's disease

NICE (2019): Crohn's disease: management NG129 (1) Please see links below for full NICE guidance.

2.1.1. NICE (2010): Infliximab and adalimumab for the treatment of Crohn's disease TA187

2.1.2. NICE (2015): Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy TA352

2.1.3. NICE (2017): Ustekinumab to treat moderately to severe Crohn's disease after previous treatment TA456

2.2. Ulcerative colitis

NICE (2019): Ulcerative colitis: management NG130 (2). Please see links below for full NICE guidance.

2.2.1. NICE (2015): Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy TA329

2.2.2. NICE (2008): Infliximab for acute exacerbations of ulcerative colitis TA163

2.2.3. NICE (2015): Vedolizumab for treating moderately to severely active ulcerative colitis TA342

2.2.4. NICE (2018): Tofacitinib for moderately to servery active ulcerative colitis TA547

2.2.5. NICE (2020): Ustekinumab for treating moderately to severely active ulcerative colitis TA633

3. Initiating treatment with a biological medicine

The choice of biologic used should be guided by clinical judgement, national and local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.

If a patient also has psoriasis or inflammatory arthritis, consider choosing a drug that is also approved under the appropriate GMMMG High Cost Drugs Pathway. Take into account patient factors such as device, dexterity, dose frequency, route of administration, likely adherence, co-morbidities, weight, and drug history.

If more than one treatment is suitable, the least expensive product should be chosen (taking into account administration costs, dosage, price per dose and treatment frequency). At the time of publication this was biosimilar adalimumab. Where biosimilars are available the best value product should be used. See GMMMG (2016): Prescribing of high cost biosimilar biological medicines.

If the least expensive product is not prescribed, the reasons why must be documented and made available to commissioners if requested.

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 on-going pharmacovigilance of the individual products.

Pharmacovigilance is essential for any new biological medicine including biosimilars and additional monitoring is indicated through the MHRA's Black Triangle Scheme. Patients prescribed a biologic should be enrolled on to the relevant biologic registry which serves data collection on the safety and effectiveness of medicines in clinical practice.

Treatment should be reviewed to assess efficacy as per NICE guidance, and thereafter at least every 12 months. See flowcharts in section 7 for a summary of the treatment pathway.

4. Dose optimisation

Dose escalation or optimisation is licensed for several drugs, although dosing adjustment is not recommended for newer subcutaneous formulations of infliximab and vedolizumab. Off-label escalation of infliximab is now a routine clinical practice in GM. See algorithm C for guidance on anti-TNF dose adjustment following poor or loss of response.

Drug	**Standard maintenance dose (3)**	**Optimised dose** (3) (4)	
		Crohn's disease	**Ulcerative colitis**
Adalimumab (SC)	40 mg every 2 weeks	40 mg every week, or 80 mg every 2 weeks*	
Infliximab (IV)	5 mg/kg every 8 weeks	If response poor or lost* *5 mg/kg every 6 weeks* or *5mg/kg every 4 weeks* or 10mg/kg every 8 weeks or *10mg/kg every 6 weeks* or *10mg/kg every 4 weeks*	If response poor or lost* *5 mg/kg every 6 weeks* or *5mg/kg every 4 weeks* or *10mg/kg every 8 weeks* or *10mg/kg every 6 weeks* or *10mg/kg every 4 weeks*
Infliximab (SC)	120mg every 2 weeks	No data – not recommended	
Golimumab (SC)	Ulcerative colitis only: 50 mg every 4 weeks or 100 mg every 4 weeks if body weight ≥80 kg	Not licensed in Crohn's disease	100 mg every 4 weeks, if inadequate response at week 6 or body weight ≥80 kg*
Tofacitinib (PO)	Ulcerative colitis only: 5 mg twice daily	Not licensed in Crohn's disease	10 mg BD for an additional 8 weeks, followed by 5 mg BD, if adequate response not achieved in first 8 weeks**
Ustekinumab (SC)	90 mg every 12 weeks	90 mg every 8 weeks, if response lost with dosing every 12 weeks **NB escalation off-label is not routinely commissioned**	
Vedolizumab (IV)	300 mg every 8 weeks	300 mg every 4 weeks, if response lost with dosing every 8 weeks	
Vedolizumab (SC)	108 mg every 2 weeks	No data – not recommended	

IV – intravenous; PO - oral; SC – subcutaneous; *off-label regimens in italics*

** Use 10 mg twice daily as maintenance for the shortest duration possible. Not recommended in patients who have known venous thromboembolism risk factors unless there is no suitable alternative treatment available. (3) **Continued on next page.**

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. (5)

5. Biosimilars

Use of biosimilars has become routine clinical practice. All NICE guidance on biologics applies to biosimilar medicines. The European Crohn's and Colitis Organisation (ECCO) have published a biosimilar position statement which states:

- When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics.
- Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.
- Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.
- 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 Celltrion).

6. Individual funding requests (IFRs)

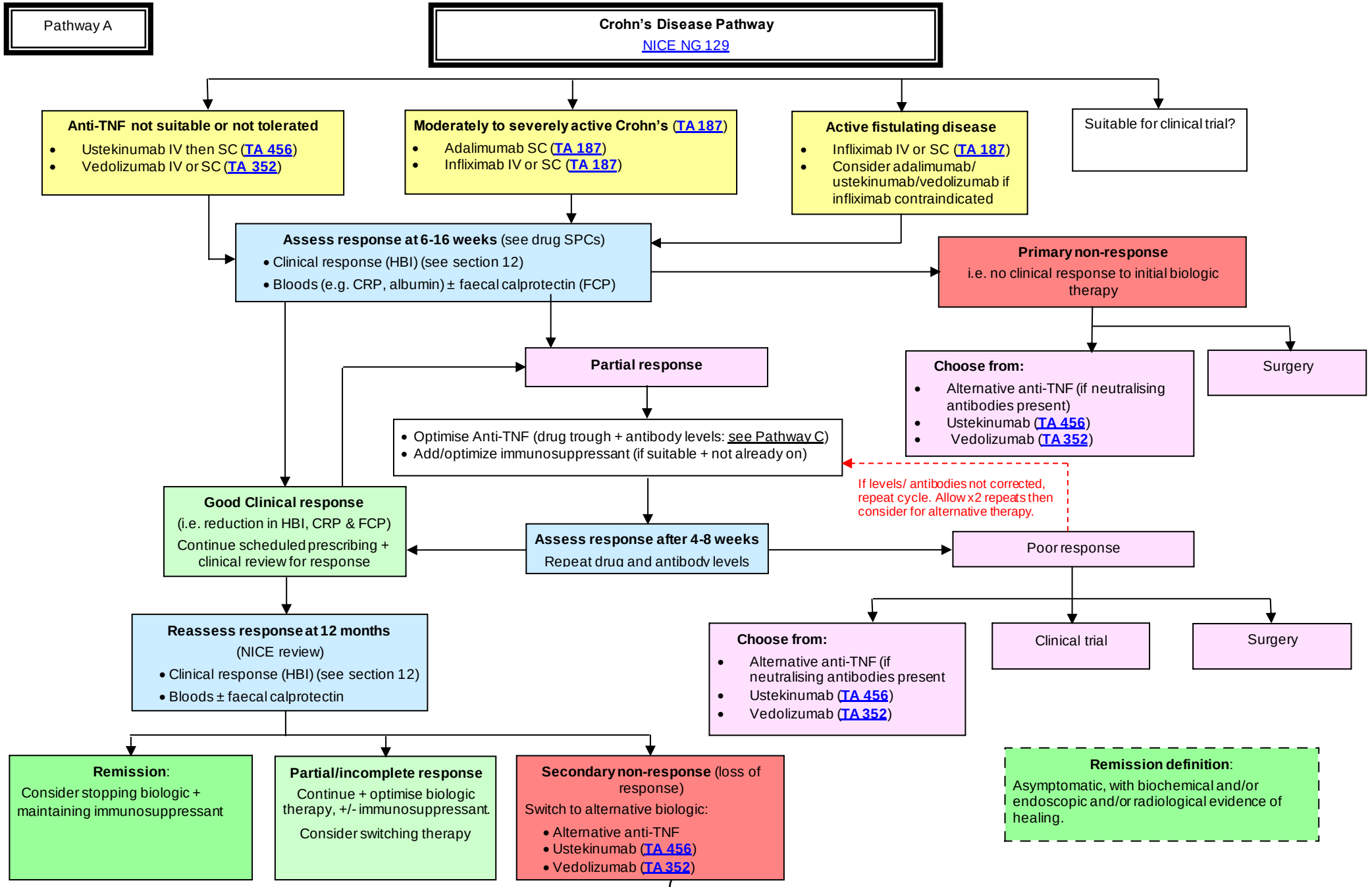
- Up to four high cost drugs for treatment of Crohn's disease will be routinely commissioned, if prescribed in accordance with this pathway.
- Fifth and subsequent high cost drugs will require discussion and approval by a multi-disciplinary team (MDT) comprising at least two consultants (including other specialties as appropriate), a specialist nurse and/or a specialist pharmacist. No limit will be placed on the number of available drugs, but the MDT must be satisfied that continued treatment is in the best interests of the patient. IFRs will not be required but, where available, Blueteq forms must be completed and MDT approval must be documented.
- Treatment options outside of this pathway will NOT require an IFR prior to treatment, if the intervention have been recommended by a NICE TA but not yet included in the pathway since last update.
- Only truly exceptional cases will be considered via IFR route and exceptionality must be demonstrated in the submission by treating clinician. **Exhausting the treatment options in this pathway does not automatically establish exceptionality**. IFR must include details of all previous treatments with outcomes using disease-appropriate scores, reasons for discontinuation and list alternative interventions including non-pharmacological treatments.
- Other treatments outside of the pathway and for non-routinely commissioned interventions will require MDT discussion and internal provider approval (with involvement of financial representative where appropriate). Patients should be monitored for response to treatment and reviewed regularly. The decisions and treatment outcomes must be clearly recorded and available for monitoring and auditing purposes.
- Requests for urgent treatment of acute severe ulcerative colitis with high doses of infliximab (see section 10.3.2.) are considered a rescue intervention and do not require an IFR. A Blueteq notification form for use of infliximab in acute exacerbation should be filled in retrospectively.

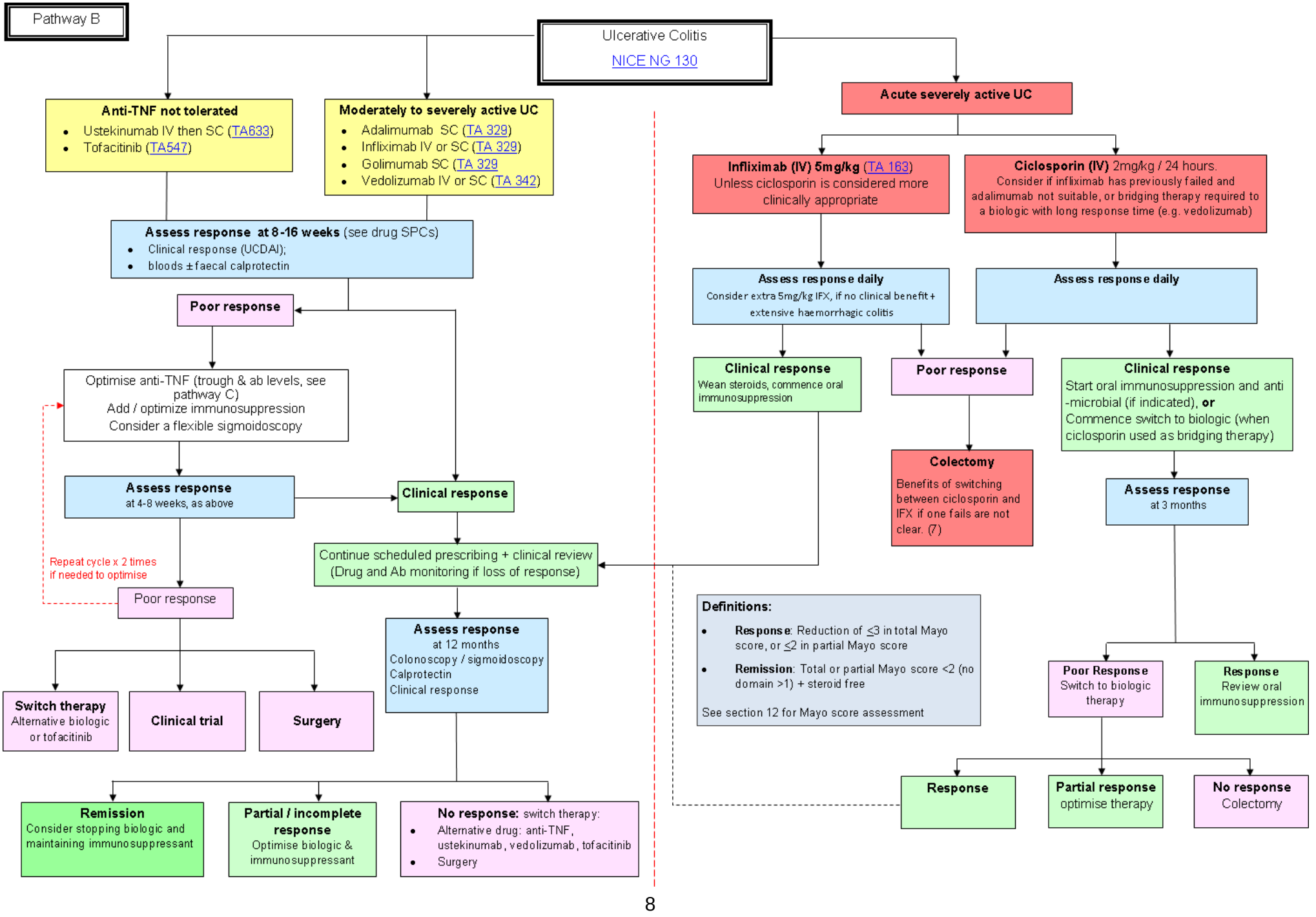
7. Blueteq

Blueteq forms which comply with these pathways are available. Where Blueteq has been introduced to the trust as part of the contractual arrangements, funding approval for the tariff excluded high cost drugs will be required by submission of the relevant Blueteq form prior to treatment administration. The Blueteq forms contain a list of relevant criteria that the patient must meet in order to secure funding. Any patients who do not meet these criteria will require an IFR.

NB: A Blueteq notification form for use of infliximab in acute exacerbation of ulcerative colitis can be filled in retrospectively.

8. GM HCD Pathway for inflammatory bowel disease




Pathway B
Ulcerative Colitis
NICE NG 130
Anti-TNF not tolerated
Ustekinumab IV then SC (TA633)
Tofacitinib (TA547)
Moderately to severely active UC
Adalimumab SC (TA 329)
Infliximab IV or SC (TA 329)
Golimumab SC (TA 329
Vedolizumab IV or SC (TA 342)
Assess response at 8-16 weeks (see drug SPCs)
Clinical response (UCDAI);
bloods ± faecal calprotectin
Poor response
Optimise anti-TNF (trough & ab levels, see pathway C)
Add / optimize immunosuppression
Consider a flexible sigmoidoscopy
Assess response
at 4-8 weeks, as above
Clinical response
Repeat cycle x 2 times if needed to optimise
Poor response
Continue scheduled prescribing + clinical review
(Drug and Ab monitoring if loss of response)
Switch therapy
Alternative biologic or tofacitinib
Clinical trial
Surgery
Assess response
at 12 months
Colonoscopy / sigmoidoscopy
Calprotectin
Clinical response
Remission
Consider stopping biologic and maintaining immunosuppressant
Partial / incomplete response
Optimise biologic & immunosuppressant
No response: switch therapy:
Alternative drug: anti-TNF, ustekinumab, vedolizumab, tofacitinib
Surgery
Acute severely active UC
Infliximab (IV) 5mg/kg (TA 163)
Unless ciclosporin is considered more clinically appropriate
Ciclosporin (IV) 2mg/kg / 24 hours.
Consider if infliximab has previously failed and adalimumab not suitable, or bridging therapy required to a biologic with long response time (e.g. vedolizumab)
Assess response daily
Consider extra 5mg/kg IFX, if no clinical benefit + extensive haemorrhagic colitis
Assess response daily
Clinical response
Wean steroids, commence oral immunosuppression
Poor response
Clinical response
Start oral immunosuppression and anti-microbial (if indicated), or
Commence switch to biologic (when ciclosporin used as bridging therapy)
Colectomy
Benefits of switching between ciclosporin and IFX if one fails are not clear. (7)
Assess response
at 3 months
Definitions:
Response: Reduction of ≤3 in total Mayo score, or ≤2 in partial Mayo score
Remission: Total or partial Mayo score <2 (no domain >1) + steroid free
See section 12 for Mayo score assessment
Poor Response
Switch to biologic therapy
Response
Review oral immunosuppression
Response
Partial response
optimise therapy
No response
Colectomy

Pathway C

Loss or poor response to biologic anti-TNF therapy for CD or UC

* NB: Anti-TNF drug levels and antibody levels may vary depending on the assay or centre used for analysis

Confirm active IBD flare:

- Calprotectin
- Bloods (routine; antiTNF Ab + drug trough)
- Endoscopy / radiology
- Exclude alternative pathology (see box, right)

Exclude alternative pathology:

- Stricture
- Cancer
- Infection
- IBS

Anti-TNF drug trough level **undetectable**

Anti-TNF drug antibodies detectable

Drug being neutralised by neutralizing drug antibodies

a. Anti-TNF antibody level > 10*
   - Consider stopping anti-TNF
   - Switch drug: - another anti-TNF
     - Ustekinumab
     - Vedolizumab
     - Alternative immunosuppressant

b. Anti-TNF antibody level < 10*
   - Add in and/or optimise immunosuppressant
   - Increase dose/frequency of anti-TNF

Anti-TNF drug antibodies undetectable

Insufficient drug available: check adherence

a. Poor adherence: improve if possible.

b. Good adherence: suggests accelerated drug consumption/clearance
   - Reduce time between doses
   - Increase drug dose

Anti-TNF drug trough level **detectable***

- Target infliximab drug trough level = 7 - 10
- Target adalimumab drug trough level = >5 (suggest aim: 5 - 10)

NB: drug levels may vary depending on assay or lab used

Low drug trough + antibody < 40 or undetectable

Increase drug dose / frequency

or, add in immunosuppression

or, switch anti-TNF/biologic

Low drug trough + antibody > 40

Consider switch to an alternative anti-TNF or other biologic

Trough level within or above therapeutic range + loss of clinical response

Non-TNF driven disease: switch to a non anti-TNF therapy e.g. ustekinumab or vedolizumab

Antibodies:

- The precise level of antibody significance is currently undefined. A low level of antibody can be clinically significant, if the antibody is neutralizing the drug.
- Antibodies can be reduced by immunosuppression or anti-TNF dose adjustments
- An antibody level >40 is unlikely to be overcome by immunosuppression or anti-TNF dose adjustments.

If adjusting an anti-TNF dose or adding in a new immunosuppressant:

→ repeat clinical review and antibody + drug trough level testing after 2-4 months:

- If response: continue therapy and review after 6 months
- If partial response: optimise biologic therapy (further Ab + drug level testing) + immunosuppression
- If no response: consider entry into a clinical trial / alternative biologic therapy / surgery

9. Contraindications, special warnings and precautions for treatment with drugs

9.1. Cautions and contraindications

Cautions, contraindications, and special warnings to use of systemic agents for IBD are detailed in the individual summaries of products characteristics (SPCs), which are available from www.medicines.org.uk. (3) Prescribers should consult the relevant SPC to inform clinical decision-making for individual patients.

9.2. Additional safety considerations

The MHRA has published Drug Safety Updates relating to several of the drugs included in this pathway, all of which are available from www.gov.uk/drug-safety-update:

- Tofacitinib (Xeljanz▼): new measures to minimise risk of major adverse cardiovascular events and malignancies, October 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; March 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.
- Live attenuated vaccines: avoid use in those who are clinically immunosuppressed; April 2016
- Ustekinumab (Stelara): risk of exfoliative dermatitis; January 2015. Be alert for signs and symptoms of exfoliative dermatitis or erythrodermic psoriasis. Start appropriate treatment promptly if these occur and stop ustekinumab if exfoliative dermatitis is suspected to be an adverse reaction to ustekinumab.
- Tumour necrosis factor alpha inhibitors; December 2014. Risk of tuberculosis - screen all patients before starting treatment and monitor them closely.

10. Special situations

10.1. Therapeutic drug monitoring and antibody testing (where available / commissioned)

The pathways include three tumour necrosis factor-alpha inhibitors (anti-TNFs): infliximab, adalimumab and golimumab. Failure to respond and loss of clinical effect to anti-TNF therapy are both common in gastroenterology patients. (6; 7)

Currently, therapeutic drug monitoring (TDM) and antibody testing in IBD patients is available for infliximab and adalimumab and is recommended for patients exhibiting primary non-response and where a secondary loss of response to therapy is suspected as it can help to identify specific reasons for treatment failure and aid clinical decision making. (6; 7) See pathway C above for details.

As a biologic therapy optimisation initiative, proactive TDM (i.e. where there is no loss of response) can provide evidence for the need for continued anti-TNF therapy in individual patient and give reassurance to patients following a switch to biosimilar via demonstrable evidence of unaltered drug efficacy.

The blood sample for anti-TNF TDM should be collected prior to administration of the next scheduled dose of the drug to allow investigation of trough levels. The reference ranges for anti-TNF TDM may vary slightly between labs depending on the assay used.

Currently, guidance relating to antibodies and drug levels for golimumab and biologics with different mechanism of action (ustekinumab and vedolizumab) is not available.

There may be variation across GM in extent of TDM application, particularly of the proactive intervention.

10.2. Switching between treatments with different biologics

Recommendations differ on the need for a washout period when switching from one biologic to another. A theoretical risk for increased susceptibility to infection has been proposed if washout time is not adequate between biologic therapies. However, there is very little published data on this topic. The half-life of the drug (table 1), clinical circumstances of the individual patient and drug levels should be considered in each case to aid decision making.

10.3. High risk patients

10.3.1. Early onset Crohn's disease

The course of Crohn's disease may be predicted by clinical factors at diagnosis and/ or at endoscopy.

Onset before 40 years of age is a risk factor for a poor disease outcome. (6) Aggressive Crohn's disease is characterised by features such as increased relapse rates, and hospital admissions, the development of penetrating or stricturing disease, abscesses, or the need for surgery. (8) The treating specialist could consider early introduction of high cost drug therapy in those with early onset and at least two of the following factors:

- Age under 40 years at diagnosis
- Extensive small bowel disease
- Deep and extensive colonic ulceration
- Perianal / rectal disease
- Stricturing or penetrating disease
- More than 5kg unintentional weight loss pre-diagnosis, or low body mass index
- The requirement of corticosteroid at diagnosis
- Steroid dependency
- Smoking (encourage smoking cessation; be aware that passive smoking and light smoking carry the same risk as heavy smoking) (9)

The decision to initiate early biological or JAK inhibitor therapy should also consider factors such as impact on work or other activities of daily living, and availability of other treatment options. (9)

10.3.2. Acute severe ulcerative colitis

In acute severe ulcerative colitis where infliximab rescue therapy has been necessary, an undetectable serum anti-TNF drug level corresponds with a greater colectomy risk. (10) In patients with extensive haemorrhagic colitis who have not responded to initial treatment, a higher dose of infliximab (10 mg/kg loading, or a second 5 mg/kg after 3-5 days, both unlicensed) can be considered at the discretion of the clinician in order to reduce the risk of colectomy. (10; 11) This would be an immediate rescue treatment and not an individual funding request.

10.4. Surgery

10.4.1. Perioperative risk of infection

Risk of postoperative infection may be reduced by temporarily stopping treatment with a biologic or JAK inhibitor. The safe interval remains to be determined. (8; 12) The decision to interrupt treatment should be made following a discussion between the gastroenterology and surgical teams given the specific circumstances of each individual patient.

If a patient is to undergo an **elective surgery**, consider stopping the drug 3-5 times the half-life for the relevant drug (3) (see table below). Biologic and JAK-inhibitor therapy should not delay urgent surgery.

Drug	Mean half-life	3-5 half-lives
Adalimumab	2 weeks	6 - 10 weeks
Golimumab	12 ±3 days	4 - 11 weeks
Infliximab	Median 8 - 9.5 days	4 - 7 weeks
Ustekinumab	15-32 days	6 - 23 weeks
Vedolizumab	24 days	10 - 17 weeks
Tofacitinib standard release*	3 hours	9 – 15 hours
Tofacitinib modified release*	6 hours	18 – 30 hours

* 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.

10.4.2. Postoperative recurrence of Crohn's disease

Biologic therapy should be considered for the treatment of postoperative recurrence of Crohn's disease if immunosuppression with azathioprine or 6-mercaptopurine has failed or is not tolerated, provided NICE criteria for use are met (see section 2). Biologic therapy is not normally considered for prophylactic use following surgery. Biologics should not be offered to maintain remission following complete macroscopic resection of ileocolonic Crohn's disease. (1)

10.5. Pregnancy

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 and paternal exposure if the drug is to be continued.

Women of childbearing potential should use effective contraception during treatment and continue use for the number of weeks after treatment has stopped as advised by manufacturer (see table below).

The ECCO statements on pregnancy include the following: (13)

- If conception occurs at a time of quiescent disease, the risk of relapse is the same as in non-pregnant women. Conception occurring at a time of active disease increases the risk of persistent activity during pregnancy.
- Appropriate treatment of IBD should be maintained in order to reduce the risk of disease flares during pregnancy.
- Acute flares in pregnancy carry a high risk of adverse maternal and foetal outcome and are best treated appropriately and without delay.

ECCO's pregnancy and IBD algorithm can be accessed here and further information is also available in the BSG consensus guidelines on IBD in adults. (9)

The decision to continue or stop biologic agents in pregnancy needs to be individualised, taking into account 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. For patients who stop therapy during pregnancy, re-loading with biologic therapy should be considered soon after delivery.

The data for safety of biologics and JAK inhibitors in pregnancy and paternal exposure is limited, although recently published PIANO registry investigating outcomes among pregnancies exposed versus unexposed in utero to biologics and/or thiopurines shown that for 1490 completed pregnancies in total, drug exposure did not increase the rate of congenital malformations, spontaneous abortions, preterm birth, low birth weight baby, or infections in the first year of life. However, maternal disease activity was associated with adverse outcomes. (14)

Use of a biologic therapy is not necessarily an absolute contraindication during pregnancy or breast-feeding, but individualised risk assessment is required for each patient. Anti-TNFs cross the placenta and use of infliximab and adalimumab beyond the second trimester results in neonatal levels exceeding maternal levels. This exposure can be limited by stopping treatment around gestational week 24-26 where appropriate. (13) The 2019 BGS IBD guidelines (9) suggest that for patients on anti-TNF therapy whose disease is active or at high risk of relapse, it may be advisable to continue the drug throughout, while for those with inactive disease who wish to discontinue therapy it may be reasonable to stop at the start of the third trimester. (3)

There is limited data on the use of golimumab, ustekinumab or vedolizumab in pregnancy. As for other biologics, administration during pregnancy could affect normal immune responses in the newborn.

The use of the JAK inhibitor tofacitinib is contraindicated in pregnancy. (3)

The following is adapted from the available evidence, but prescribers should be aware that guidance may change over time as the evidence base evolves.

Drug	**Time to continue contraception after treatment cessation** (3)	**Compatibility with pregnancy trimesters** (13; 9)		
		First	**Second**	**Third**
Adalimumab	5 months	Yes	Yes*	No
Golimumab	6 months	No data	No data	No data
Infliximab	6 months	Yes	Yes*	No
Ustekinumab	15 weeks	No data	No data	No data
Vedolizumab	18 weeks	No data	No data	No data
Tofacitinib	4 weeks	Contraindicated		

* UK guidance recommends stopping at 22-24 weeks in women with sustained remission. European guidance recommends 24-26 weeks.

Further information to support decision-making is available from:

- Summaries of product characteristics (www.medicines.org.uk)

- UK Teratology Information Service (UKTIS) at http://uktis.org/html/exposures_abc.html or 0344 892 0909 (Monday-Friday, 9am-5pm).

Exposures in pregnancy should be reported to UKTIS by use of their online reporting form (http://www.uktis.org/html/reporting.html) UKTIS are commissioned by Public Health England to perform national surveillance of known and emerging human teratogens across the United Kingdom.

Advice and risk assessment for individual patients may also be available by contacting a local Medicines Information service via your trust pharmacy departments.

For information on vaccination of infants exposed to anti-TNF during pregnancy see section 10.7.

10.6. Breastfeeding

There is very limited information on the excretion of biologics in breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breastfeeding child cannot always be excluded. A decision on whether to breastfeed or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman.

Adalimumab's manufacturers advise that this biologic can be used during breastfeeding. (3) Information on other drugs manufacturers' recommendations on use in lactation is available from the individual summaries of product characteristics (available from www.medicines.org.uk).

Further information may be available from the Specialist Pharmacy Service (SPS) website at www.sps.nhs.uk and in the ECCO consensus statement on reproduction and pregnancy in IBD (January 2015).

Advice and risk assessment for individual patients may also be available by contacting a local Medicines Information service via trust pharmacy departments.

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

If a biologic has been continued in pregnancy after 16 weeks gestation live vaccines should be avoided in the infant until they reach 6 months of age, after which time vaccination should be considered. (15) The live vaccinations currently included in the childhood vaccination schedule for infants aged <1 year are: (16)

- Rotavirus - all infants
- Tuberculosis - infants living in areas of the country with incidence ≥40/100,000, and infants with a parent or grandparents born in a country with incidence ≥40/100,000 (17)

Rotavirus is the most common cause of gastroenteritis in infants in the UK. (18) Although there is limited evidence of safety and efficacy in infants with immunosuppression the vaccine may be considered by the treating consultant following careful consideration of the risks and benefits and following specialist consultation as appropriate. This does not include infants with severe combined immune deficiency.

The MHRA have received reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to an anti-TNF medicine in utero; they were probably not known to be immunosuppressed at the time of vaccination. (19)

The specialist Drugs in Lactation Information Service are confident that this risk does not exist where exposure is solely through breastfeeding. Therefore, no delay in vaccination is necessary where an infant is not affected by foetal exposure. (20)

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. (21)

10.8. Vaccinations

10.8.1. Routine vaccinations

During biologic therapy, patients should receive seasonal inactivated influenza vaccine annually and pneumococcal vaccine once only. Titres may need to be measured. (3; 15) For up to date information consult the Green Book. Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor. (15)

10.8.2. 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.

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

Live vaccine	Brand name
BCG	Bacillus Calmette-Guerin Vaccine
Influenza	Fluenz Tetra®
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	Stamaril®

When a live vaccine is required by a patient on a biologic, 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 in section 10.4.1 above, page 10. For further advice please consult:

- relevant summaries of products characteristics, www.medicines.org.uk (3)
- the Green Book: Immunisation against infectious disease (15)
- specialist advice

10.9. Non-live vaccines

Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic 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 including coronavirus vaccine please refer to the appropriate summary of product characteristics (www.medicines.org.uk) or the Green Book: Immunisation against infections disease.

11. Checklist for patient screening on initiation of biologic agents and tofacitinib

Patient's name: ……..……..……..**Number:** ……..……**Consultant:** ……..…

Screening Investigations Requested in Clinic	Y/N	Initial	Results/Details
FBC/U&E/LFT/CRP			
HIV **HBV** *(surface antigen, core antibody)*. *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* **HCV** *(antibody test)* Consider **EBV, CMV** testing. *If positive result, consider Hepatology/GUM referral*			
Varicella zoster IgG (If negative inform GP and patient)			
TB screening *(g-IFN testing)* *If positive refer to Respiratory Unit*			
Chest X-ray *(within the last 6 months)* **CXR checked by/date:**			
TPMT (Before commencing azathioprine therapy)			
Consider:			
Faecal calprotectin level			
Ferritin, vitamin B12, folate levels			
Screening Questions Asked in Clinic	**Y/N**	**Initial**	**Results/Details**
Previous TB/TB contact/ recent travel to high risk countries (*details*)			
History of demyelinating disorders of the CNS *(e.g. MS)* *(details)*			
History of heart failure (NYHA class III or IV) *(details)*			
Risk of pulmonary embolism (Tofacitinib contraindicated)			
History of recurrent infection *(details)*			
History of cancer *(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 infusion reaction to any agent *(To what/type of reaction)*			
Allergy (*details*)			

Education and Funding	Initial	Details
Request for funding		
Pregnancy/breastfeeding advice given		
Influenza vaccine advice given		
Pneumococcal vaccine advice given		
Patient counselled and educated		
Patient education pack given		

Completing clinician's signature……..……..…… Date…….....

Nurse practitioner signature……..……..……..…… Date…….....

12. Crohn's disease Severity Scoring and Clinical Monitoring

HARVEY BRADSHAW	SCORE	
GENERAL WELL-BEING		Please tick your score
Very well	0	☐
Slightly below par	1	☐
Poor	2	☐
Very poor	3	☐
Terrible	4	☐
ABDOMINAL PAIN *(yesterday)*		
None	0	☐
Mild	1	☐
Moderate	2	☐
Severe	3	☐
NUMBER OF LIQUID STOOLS *(yesterday)*		.....
ABDOMINAL MASS		
None	0	☐
Dubious	1	☐
Definite	2	☐
Definite and tender	3	☐
COMPLICATIONS	None	☐
Mouth ulcer ☐	Skin Rash	☐
Sore Joints ☐	Anal fissure	☐
Sore eyes ☐	Abscess	☐
Bruising on legs ☐	New fistula	☐

Remission	<5
Mild disease	5-7
Moderate disease	8-16
Severe disease	>16

Adapted from:

Harvey R.F. and Bradshaw J.M. A simple index of Crohn's-Disease activity. *Lancet*. 1980. 1(8167):514. doi: 10.1016/s0140-6736(80)92767-1.

Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. *Clinical Gastroenterology and Hepatology* 2016;14:348–354. doi:10.1016/j.cgh.2015.06.001

13. <u>Ulcerative Colitis Severity Scoring and Clinical Monitoring/ MAYO score</u>

MAYO CRITERIA	SCORE	
STOOL FREQUENCY		**Please tick score**
Normal	**0**	☐
1-2/day more than normal	**1**	☐
3-4/day more than normal	**2**	☐
≥ 5/day more than normal	**3**	☐
RECTAL BLEEDING		
No blood seen	**0**	☐
Streaks of blood with stool less than half the time.	**1**	☐
Obvious blood with stool most of time.	**2**	☐
Blood alone.	**3**	☐
ENDOSCOPIC FINDINGS		
Normal or inactive disease	**0**	☐
Mild disease (mild friability).	**1**	☐
Moderate disease (Contact bleeding).	**2**	☐
Severe disease (spontaneous bleeding).	**3**	☐
PHYSICIAN'S GLOBAL ASSESSMENT		
Normal	**0**	☐
Mild disease.	**1**	☐
Moderate disease.	**2**	☐
Severe disease.	**3**	☐

The physician's Global Assessment acknowledges the Sub scores, the daily record of abdominal discomfort and functional assessment and other observations such as physical findings, and the patient's performance status

Full Mayo Index Score [sum of all above items]

Remission	≤2
Mild Disease	3-5
Moderate Disease	6-10
Severe Disease	11-12

Partial Mayo Index Score [sum of above items excluding endoscopic findings]

Remission =	0-1
Mild Disease	2-4
Moderate Disease	5-6
Severe Disease	7-9

Adapted from:

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987 Dec 24;317 (26):1625-9. doi:10.1056/NEJM198712243172603

Lewis JD, Chuai S, Nissel L, et al. Use of the Noninvasive Components of the Mayo Score to Assess Clinical Response in Ulcerative Colitis. *Inflammatory Bowel Disease* 2008;14:1660-1666. doi:10.1002/ibd.20520

Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining Disease Severity in Inflammatory Bowel Diseases: Current and Future Directions. *Clinical Gastroenterology and Hepatology* 2016;14:348–354. doi:10.1016/j.cgh.2015.06.001

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