Biologics Guidelines for Inflammatory Bowel Disease in Adults

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Endorsing Body: NHS Lanarkshire Gastroenterology Inflammatory Bowel Disease

Governance or Assurance Committee: Area Drug and Therapeutics Committee

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## Change Record

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<th>Actioned by</th>
<th>Summary of Changes</th>
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<tr>
<td>8/5/2018</td>
<td>Deborah Lyons Biologics Nurse Specialist</td>
<td>Initial version</td>
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## Approvals

This document must be approved by the following before distribution

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<td>Dr Marc Cram</td>
<td>Consultant Gastroenterologist</td>
<td>8/5/18</td>
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<td>Dr Diarmid Sutherland</td>
<td>Consultant Gastroenterologist</td>
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1. Background

These pathways are to be used as guidelines in the initiation and maintenance of biologic agents in the management of inflammatory bowel disease (IBD). These pathways have been written using up to date published research and evidenced based medicine.

This pathway is adapted and developed from Manchester University NHS Foundation Trust- Biologics Pathway, with permission gained from Dr Scott Levinson BSc MBChB MRCP PhD, Consultant Gastroenterologist to utilise and adapt for NHS Lanarkshire.

This has been a clinical project implemented by NHS Lanarkshire and a joint project between the Gastroenterology departments of the three Lanarkshire hospitals - University Hospital Wishaw, University Hospital Hairmyres and University Hospital Monklands.
2. NICE Guidance

The links to relevant NICE guidance are listed below. Any new high cost drugs that are approved by NICE between NHS Lanarkshire IBD pathway iterations will be considered for placement in this pathway. The use of any new NICE approved high cost drugs prior to inclusion in the pathway will be allowed, 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.

All drugs discussed in the following NICE Guidelines have been SMC (Scottish Medicine Consortium) approved for use in NHS Scotland further information can be accessed on their website (43).

2.1. Crohn’s disease

NICE (2012 - updated 2016): Crohn's disease: management CG152 (1)

a) NICE (2010): Infliximab and adalimumab for the treatment of Crohn's disease TA187(2)

**Infliximab** and **adalimumab**, are recommended as treatment options for adults with severe active Crohn’s disease whose disease has not responded to conventional therapy (immunosuppressive and/or corticosteroid) or who are intolerant of or have contraindications to such therapy.

**Severe active Crohn’s disease** is defined as very poor general health, plus >1 symptom of: weight loss, fever, severe abdominal pain, and frequent (3-4 or more) diarrhoeal stools daily. People with severe active Crohn’s disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease.

This clinical definition normally, but not exclusively, corresponds to a **Crohn’s Disease Activity Index (CDAI)** score > 300, or a **Harvey-Bradshaw score** (see sections 9/10) of >8.

**Infliximab** is recommended as treatment option for people with active fistulising Crohn’s disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy.

Biologic treatment should normally be started with the less expensive drug as per: Healthcare Improvement Scotland: Biosimilars Medicines: A National Prescribing Framework 2015(3).

**Infliximab or adalimumab** should be given until treatment failure, or the need for surgery, or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether on-going treatment is still clinically appropriate. Treatment should only be continued if there is clear evidence of on-going active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary.

People who continue treatment should have their disease reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

A trial withdrawal should be considered in patients in stable clinical remission.

People whose disease relapses after treatment is stopped should have the option to start treatment again.
b) NICE (2015): Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy
TA352(4)

Vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease only if:

- a tumour necrosis factor-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment), or:
- a tumour necrosis factor-alpha inhibitor cannot be tolerated or is contraindicated.

Vedolizumab should be given as a planned course of treatment until it stops working or surgery is needed, or until 12 months after the start of treatment, whichever is shorter.

At 12 months, people should be reassessed to determine whether treatment should continue. Treatment should only continue if there is clear evidence of on-going clinical benefit.

People who continue vedolizumab should be reassessed at least every 12 months to decide whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

Vedolizumab is recommended only if the company provides it with the discount agreed in the patient access scheme.

Golimumab has not been included in clinical trials for Crohn's disease and is not licensed for use in Crohn's disease. Therefore is should not be considered as a treatment option for Crohn's disease, even as an individual funding request.

c) NICE (2017): Ustekinumab to treat moderately to severe Crohn's disease after previous treatment
TA456(5)

Ustekinumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active Crohn's disease, that is, for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.

The choice of treatment between ustekinumab or another biological therapy should be made on an individual basis after discussion between the patient and their clinician about the advantages and disadvantages of the treatments available. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

Ustekinumab should be given until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed in accordance with NICE's recommendations for infliximab and adalimumab for the treatment of Crohn's disease (NICE TA187) to see whether treatment should continue.

d) Golimumab has not been included in clinical trials for Crohn’s disease and is not licensed for use in Crohn’s disease. Therefore it should not be considered as a treatment option for Crohn’s disease, even as funding request.
2.2. Ulcerative Colitis

NICE (2013): Ulcerative colitis: management CG166(6)

a) NICE (2015): Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy TA329(7)

Infliximab, adalimumab and golimumab are recommended, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy (e.g. corticosteroids, mercaptopurine or azathioprine), or who cannot tolerate them, or who have a medical contraindication for such therapies.

The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available.

This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen.

Therapy should be given as a planned course until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter.

They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation including endoscopy if necessary.

Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.

People who continue treatment should be reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

Consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

b) NICE (2008): Infliximab for acute exacerbations of ulcerative colitis TA163(8)

Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis. It is only recommended in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient. Infliximab in this guidance relates to only an induction course of three doses of infliximab.

Treatment of acute exacerbations of UC with infliximab or ciclosporin should be the decision of the responsible gastroenterologist.

In line with NICE TA 329(7), therapy in the treatment of acute exacerbations of UC should be given as a planned course until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter.

Patients should continue treatment beyond this only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation including endoscopy if necessary.

People who continue treatment should be reassessed at least every 12 months to determine whether on-going treatment is still clinically appropriate.

A trial withdrawal from treatment for all patients who are in stable clinical remission should be considered. People whose disease relapses after treatment is stopped should have the option to start treatment again.
c) NICE (2015): Vedolizumab for treating moderately to severely active ulcerative colitis TA342(9)

Vedolizumab is recommended as an option for treating moderately to severely active ulcerative colitis only if the company provides vedolizumab with the discount agreed in the patient access scheme. Vedolizumab should be given until it stops working or surgery is needed.

At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of on-going clinical benefit. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.
3. Biosimilars
In February 2016 the British Society of Gastroenterology (BSG) published guidance on the use of biosimilar infliximab in inflammatory bowel disease:

BSG(2016) Guidance on the Use of Biosimilar Infliximab in Inflammatory Bowel Disease (10)

The guidance states that there is sufficient data from observational studies to show that safety and clinical efficacy of biosimilar infliximab are comparable to the originator drug, with similar immunogenicity, and that switching from Remicade to a biosimilar is also safe and effective.

Healthcare Improvement Scotland: Biosimilars Medicines: A National Prescribing Framework 2015(3)(11) is available for adoption by gastroenterology centres using this pathway.

a) Initiating treatment with a biologic
- The choice of biologic used should be guided by clinical judgement, national or local guidance, and the overall value proposition offered by the individual medicines. The rationale for choice should be documented.

- If more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).

- When the biologic treatment has been selected, the least expensive product, either biosimilar or originator should be prescribed.

- If the least expensive product is not prescribed, the reasons why must be documented and made available if required.

- Where NICE has already recommended the originator biological medicine, the same guidance will apply to the biosimilar medicine.

- In line with MHRA guidelines: Gov.uk/drug-safety-update/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 black triangle. Patients prescribed a biologic should be enrolled on to relevant registries which gather data on the safety and effectiveness of the medicine in clinical practice.

b) Changing from originator to a biosimilar
- There is accumulating 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 only be done after discussion and agreement with individual patients with an explanation for the reason for changing.

- Changing a patient on a biologic originator medicine to a biosimilar should be done at the point of prescribing.

- There should be no automatic substitution of a biologic with a biosimilar at the point of dispensing or administration.
4. Unlicensed Medicine Request/Funding forms

As per NHS Policy for Unlicensed medicine (44): request forms must be submitted where appropriate, furthermore prescribers have a responsibility to advise the patient that they are being treated with an unlicensed / off-label medicine.

The prescriber should provide the patient with accurate and clear information that meets their needs, including information on side effects.

For use of an unlicensed medicine the prescriber should obtain written informed consent from the patient/carer. Patients will be asked to sign a duplicate consent form (patient unlicensed medicine consent form 0905) once the therapy has been explained; one copy is retained in the medical notes and the second copy sent to pharmacy with the prescription.

All Request forms are available on NHS Lanarkshire Intranet - FirstPort
- Form B – Request for a Medicine Which Lacks Substantive Funding
- Form C – Request to use an Unlicensed Medicine

In the event of Prescribing/Dose Escalation:- Consultants/Prescribers should complete and submit the relevant sections of the appropriate form(s), as shown below, to Pharmacy for processing.

Where this involves further funding, when pharmacy staff have completed the costing section, the form is then to be sent to the Chief of Medical Services for authorisation.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Diagnosis</th>
<th>Dosage</th>
<th>Escalation</th>
<th>Form C - Request to use an Unlicensed Medicine</th>
<th>Form B- Request for a Medicine Which Lacks Substantive Funding</th>
<th>Unlicensed Medicine Consent Form 0905</th>
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<tr>
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<td>40mg 2weekly (Standard dose)</td>
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<td>Infliximab</td>
<td>UC/CD</td>
<td>7.5mg/Kg</td>
<td>8 weekly</td>
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<tr>
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* These products are included in the group of MABs that do not require individual funding when initiated, so where there is any dose change funding is not required
5. Checklist for Patient Screening on Initiation of Biologic Agents

As per - West of Scotland Regional Planning Group, Efficiency & Productivity Workstream, Prescribing Steering Group, Gastroenterology Prescribing Group

Biological therapy in IBD patients - Pre-initiation checklist

<table>
<thead>
<tr>
<th>Date</th>
<th>Outcome</th>
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- MDT discussion
- Patient Counselling (as below)
- Detailed patient history to determine previous TB status or recent contact
- CXR/ T-spot/respiratory referral if indicated
- Vaccination/Smear/HPV/VZV history review
- Co-morbidity history taken and no contraindications to treatment (see below)
- Starting weight
- Hepatitis B, C, HIV history, counselling and serology
- Varicella serology and advice given if non-immune
- Drug funding approved
- Day unit/ Homecare arranged
- Written drug information to patient
- GP/ECS informed
- Written consent to treatment (as below)

Checklist completed by …………………………. on …………………

Patient counselling

- indication, compliance and monitoring and alternative therapies
- side effects including lymphoma, serious infection, demyelination, allergic reactions, worsening heart failure
- risk factor modification including smoking cessation, sunlight protection, smear surveillance, colonoscopy surveillance
- family planning advice
- vaccinations – recommend pneumococcal vaccine, Hep B vaccine if at risk occupation, annual influenza vaccine, avoid live vaccines.
- seeking medical attention if side effects, treatment failure, infections, exposure to VZV if non-immune.

Cautions/contraindications to therapy with Biological treatment

- Active sepsis
- Active cancer
- Pregnancy/breast feeding
- Demyelinating disorder
- Moderate to severe heart failure
- Significant hepatic/renal impairment
- Structuring with evidence of intestinal obstruction
6. Contraindications, special warnings and precautions for biologic agents

a) Contraindications to anti-TNF’s (infliximab, golimumab, adalimumab)(12)(13)(15)

Moderate or severe heart failure (NYHA class III/IV heart)
Tuberculosis* or other severe infections such as sepsis, abscesses, and opportunistic infections
History of hypersensitivity to the active substance, to other murine proteins, or to any of the excipients

*In acute severe Ulcerative Colitis waiting for result of Quantiferon test to rule out tuberculosis may not be possible. The decision should be made by the consultant gastroenterologist with referral for respiratory opinion if appropriate.

Special warnings and precautions for use with infliximab(12)
Medicines.org.uk: Infliximab special warnings and precautions

Special warnings and precautions for use with golimumab (15)
Medicines.org.uk: Golimumab special warnings and precautions

Special warnings and precautions for use with adalimumab(13)
Medicines.org.uk: Adalimumab special warnings and precautions

Contraindications to vedolizumab

Hypersensitivity to vedolizumab or to any of the excipients.
Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML)

Special warnings and precautions for use with vedolizumab(14)
Medicines.org.uk: vedolizumab special warnings and precautions

Contraindications to Ustekinumab

Hypersensitivity to ustekinumab active substance or to any of the excipients
Tuberculosis* or other severe infections such as sepsis, abscesses, and opportunistic infections
Latex sensitivity - The needle cover on the syringe in the STELARA pre-filled syringe is manufactured from dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Special warnings and precautions for use with ustekinumab(16)
Medicines.org.uk: ustekinumab special warnings and precautions
b) Hypersensitivity Reactions and Infusion related reactions

Hypersensitivity Reactions

Hypersensitivity Reactions (HSR) to monoclonal antibodies, which may vary in severity from mild to life-threatening, can lead to the discontinuation and replacement by alternative agents that are often less effective, more toxic and/or more expensive. (17)

Immediate HSRs occur while the medication is being administered (such as during the infusion of monoclonal antibody) or within the first hour after administration and they are clinically characterized by flushing, urticaria, angioedema, laryngeal oedema, gastrointestinal symptoms (nausea, vomiting and diarrhoea), respiratory symptoms (rhinoconjunctivitis, bronchospasm) and anaphylaxis, with or without cardio-vascular collapse which can lead to death. (17)

Suggested Algorithm for infusion reactions (18)

Mild IR
- Mild transient event
- Pruritus
- Flushing
- Myalgia
- Fever<38°C

Attenuate infusion rate

Resume infusion rate

Moderate IR
- Chest tightness
- Urticaria
- Hypertension
- Fever>38°C

Interrupt the infusion

Urticaria?
- IV Chlorphenamine /Hydrocortisone

Fever?
- Oral Paracetamol 500-1000mg

Resume infusion
- Graded dose challenge
- Start 10ml/hr
- Increase to MAX tolerated

Severe IR
- Brochospasm
- Angioedema
- Hypotension

Promptly and simultaneously
* Stop Infusion
* Call for help
* IM Epinephrine 0.5mg 1:1000
* Record time, repeat in 5min X3
* Supine position; elevate legs

Next Immediate Steps
* Oxygen face mask
* Wide bore IV access
* NACl 0.9% 1000-2000ml
* Be ready to initiate CPR
**Infusion related reactions**

The majority of IFX-related infusion reactions are thought to result from rapid, infusion rate-related cytokine release from the affected immune cells. In these cases, temporary reduction/titration of the infusion rate is regarded as the most effective, and often the only, required intervention (18).

Temporary reduction/titration of the infusion rate is often the only intervention required in cases of mild and transient immediate infusion reactions. In cases of moderate infusion reactions, temporary interruption of the infusion is necessary in most instances, together with administration of medications (Corticosteroids/Anti-histamine/Anti-Pyretic) to control the symptoms (18).

In the event of a mild/moderate reaction that has resolved with 100mg IV Hydrocortisone/10mg IV Chlorphenamine /Oral Paracetamol and medical decision made to re-challenge , recommence drug 30mins after initial reaction at the appropriate re-challenge rates.

<table>
<thead>
<tr>
<th>Initial graded re-challenge rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial 15 min</td>
</tr>
<tr>
<td>Next 15 min</td>
</tr>
<tr>
<td>Next 15 min</td>
</tr>
<tr>
<td>Next 15 min</td>
</tr>
<tr>
<td>Next, until infusion is complete</td>
</tr>
</tbody>
</table>

**Management of late Infusion reactions**

Due to the fact of the rare occurrence of late infusion reactions it precludes randomised clinical trials as to how they should be managed. Antihistamines are often suggested for symptomatic relief of pruritus; paracetamol serves for symptomatic relief of low-grade fever and arthralgias. Patients with higher fever, severe arthralgias/ arthritis, or extensive rash/pruritus often require a short course of oral corticosteroids; intravenous corticosteroids can be considered in acutely ill patients (18).

c) **Blood Monitoring Resulting In Treatment being Withheld**

<table>
<thead>
<tr>
<th>Blood test monitoring</th>
<th>Parameter</th>
<th>Frequency</th>
<th>Lab result</th>
<th>Action</th>
</tr>
</thead>
</table>
|                       | FBC       | At each induction dose | WCC<3. 5x10^9/L  
Neut<2.0x10^9/L  
Platelets<100x10^9/L |
Rapid fall or consistent downward trend | Stop drug & discuss  
Recheck weekly until stable or recovers & discuss |
|                       | LFT       | As FBC  | ALT or Alk Phos>double the upper limit of normal range | Stop drug & discuss |
|                       | U&E       | As FBC  | Creatinine>double patient’s baseline | Stop drug & discuss |
7. Special situations

a) Drug and antibody testing (where available / commissioned)
Loss of clinical effect to anti-TNF therapy is common (19). The intensification of therapy in this event has significant cost implications.

Currently, guidance relating to antibodies and drug levels for ustekinumab, golimumab and vedolizumab is not available.

Anti-TNF trough and antibody testing is recommended when a loss of response to therapy is suspected. Measurement of drug trough levels and antibody levels may help to identify specific reasons for therapeutic failure to aid clinical decision making (20)(21).

Anti-TNF drug and antibody levels may also be suggested prior to switching a patient’s therapy to a biosimilar medicine. This is to firstly identify the on-going benefit of anti-TNF therapy in an individual, and secondly to reassure patients following a medication switch that drug efficacy had not altered (10).

The blood sample for anti-TNF drug and antibody trough levels should be collected prior to administration of the next scheduled dose of the drug.

The reference ranges for anti-TNF antibody and drug trough levels may vary slightly depending on the assay used.

b) Infliximab Accelerated rates
Due to increasing safety and efficacy of Accelerated rates of Infliximab infusions (22), where appropriate patients can be placed on the following Accelerated rates if tolerated.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Infusion rate</th>
<th>Monitoring Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1-4</td>
<td>2-hour infusion</td>
<td>2-hour monitoring period</td>
</tr>
<tr>
<td>Cycle 5-9</td>
<td>1-hour infusion</td>
<td>1-hour monitoring period</td>
</tr>
<tr>
<td>Cycle 10</td>
<td>30-minute infusion</td>
<td></td>
</tr>
</tbody>
</table>

c) Switching between treatments
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.

d) High risk patients
I. 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.

Aggressive Crohn’s disease causes increased relapse rates, increased admissions to hospital, the development of penetrating disease or structuring disease or abscesses plus the need for surgery.

A specialist could consider potential disease modifying therapy in those with early onset and at least two of the following factors (23).

- Extensive small bowel disease
- Deep and extensive colonic ulceration
- Perianal / rectal disease
- Strictureing disease
- >5kg weight loss pre-diagnosis
- The requirement of corticosteroid at diagnosis
- Steroid dependency
- Smoking (encourage smoking cessation)

http://www.e-guide.ecco-ibd.eu/diseaseinfo/prognostic-factors

II. 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(20). In patients with extensive haemorrhagic colitis who have not responded to treatment, a higher dose of infliximab (10mg/kg loading, or a second 5mg/kg at 24-48 hours) could be considered at the discretion of the clinician as an Individual Funding Request.

e) Surgery

I. Peri-operative risk

Potential post-operative infection may be reduced by temporarily stopping a patient’s biologic treatment. The decision to do so should be made following a discussion between the gastroenterology and surgical teams given the specific circumstances of each individual patient (24).

The safe interval remains to be determined (24). If treatment should be stopped prior to elective surgery, if possible consider stopping the drug 3-5 times the half-life for the relevant drug. Recent biologic therapy should not delay urgent surgery.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Half Life (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>12-14</td>
</tr>
<tr>
<td>Infliximab</td>
<td>9</td>
</tr>
<tr>
<td>Golimumab</td>
<td>12-14</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>25</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>15-32</td>
</tr>
</tbody>
</table>

Table 1*summary of product characteristics(SPC) (12-16) www.medicines.org.uk

II. Post-operative recurrence

Biologic therapy should be considered for the treatment of post-operative recurrence of Crohn’s disease if immunosuppression with azathioprine/6-mercaptopurine has failed or is not tolerated (25-27). Biologic therapy is not normally considered for prophylactic use following surgery.
f) Pregnancy and Lactation

Pregnancy

ECCO guidelines on pregnancy in IBD:

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.

There is limited data for safety of biologic drugs in pregnancy and lactation.

The decision to continue 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.

In patients who stop therapy during pregnancy, consider re-loading with biologic therapy soon after delivery.

Several studies have shown that treatment with infliximab and adalimumab does not increase the risk of adverse pregnancy outcomes during the first trimester(28)(29)(30).

Transfer of anti-TNF drug across the placenta is highest in the 2nd and 3rd trimesters(28)(31)(32). Infliximab and adalimumab cross the placenta and their use 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(28)(31)(32).

There is little information on the use of golimumab in pregnancy(15)(31)(32).

There is limited amount of data on the use of vedolizumab in pregnant women. Animal studies do not indicate any harmful effects(14). Vedolizumab may be used in pregnancy only if the benefits outweigh any potential risk to mother or foetus(14).

Lactation

There is limited data on compatibility with breast feeding or with paternal exposure which is listed in the table below.

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Compatibility with breast feeding</th>
<th>Compatibility with paternal exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Yes*</td>
<td>Yes*</td>
</tr>
<tr>
<td>Golimumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Limited data

Low levels of infliximab and adalimumab can be detected in breastmilk but the level of oral absorption by the infant is unclear. Follow-up of infants exposed in utero and breastfed during maternal infliximab therapy have found no adverse effects and normal development (12) (13) (29) (30).

It is not known whether golimumab, vedolizumab or Ustekinumab are excreted in human milk or absorbed systemically after ingestion. Due to the lack of data the manufacturer does not recommend breast feeding during treatment. It is therefore not advisable to breast feed during treatment (14-16) (33-35).
g) Vaccination of infants

Any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible (32).

In the case of in utero exposure to a biologic medicine, this period should be until the infant is age 6 months, after which time vaccination should be considered (32).

MHRA have received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to a biologic medicine in utero; they were probably not known to be immunosuppressed at the time of vaccination (32).

Current vaccination strategies with non-live vaccines for infants who have been exposed to a biologic medicine in utero do not differ from those for unexposed infants (32).

The risk of a natural rotavirus infection is high. Although the vaccine is a live attenuated virus the benefit from vaccination may exceed the risk of infection. Vaccination should be discussed on an individual basis.

8. Vaccinations

a) Live Vaccines

The administration of live vaccines is contraindicated in patients on biologic agents (12-16) (36).

It is safe to administer a live vaccine 4 weeks prior to commencing biologic therapy, when necessary.

There is no contra-indication 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.

<table>
<thead>
<tr>
<th>Live Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guerin Vaccine</td>
</tr>
<tr>
<td>Influenza</td>
<td>Fluenz Tetra®</td>
</tr>
<tr>
<td>Measles, Mumps and Rubella combined vaccine (MMR)</td>
<td>MMRvaxPRO®, Priorix®</td>
</tr>
<tr>
<td>Poliomyelitis (Live oral vaccine)</td>
<td>Poliomyelitis Vaccine, live (oral) GSK OPV</td>
</tr>
<tr>
<td>Rotavirus (Live oral vaccine)</td>
<td>Rotarix®</td>
</tr>
<tr>
<td>Typhoid (Live oral vaccine)</td>
<td>Vivotif®</td>
</tr>
<tr>
<td>Varicella-Zoster Vaccine</td>
<td>Varilrix®, Varivax®, Zostavax®</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Stamaril®</td>
</tr>
</tbody>
</table>

When a live vaccine is required by a patient on a biologic, the cessation of treatment may permit a necessary vaccination to be administered. The table below shows the recommended time period required to elapse for each biologic therapy, prior to the administration of a live vaccination. These times are based on the half-life of each drug.
<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time to elapse before giving a live vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2 months</td>
</tr>
<tr>
<td>Golimumab</td>
<td>3 months</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>4 months</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>4 months</td>
</tr>
</tbody>
</table>

For patients established on a conventional immunosuppressant, e.g. azathioprine, treatment should be stopped for 6 months before the administration of a live vaccine (37). Therapy may then be restarted 2 to 4 weeks after the administration of the live vaccine.

b) Non-live Vaccines
Non-live vaccines are deemed safe to administer to people on immunosuppressant and on biologic therapies. Pneumococcal vaccine should be given 2-4 weeks before starting a biologic as response after starting treatment can be poor.

The following table gives a list of non-live vaccines available in the UK.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera Vaccine (Oral preparation only)</td>
<td>Dukural®</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Given as combined adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation.</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Avaxim®, Epaxal®, Havrix Monodose®, Vaqta Paediatric®</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Engerix®, Fendrix®, HBvaxPRO®</td>
</tr>
<tr>
<td>Hepatitis A and B Combined</td>
<td>Ambirix®, Twinrix®</td>
</tr>
<tr>
<td>Influenza</td>
<td>Agrippal®, Begrivac®, Enzira®, Fluarix®, Fluvirin®, Imuvac®, Influvac® Sub-unit, Mastaflu®, Optafiu® and Viroflu®</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Pneumovax II® (Adults and Children over 5 years), Prevenar* (Primary childhood immunisation)</td>
</tr>
<tr>
<td>Poliomyelitis (Injection)</td>
<td>Inactivated Poliomyelitis Vaccine (non-proprietary) IPV</td>
</tr>
<tr>
<td>Meningococcal Group C</td>
<td>Menjugate Kit®, NeisVac-C®</td>
</tr>
<tr>
<td>Meningococcal polysaccharide A,C, W135 and Y vaccine</td>
<td>ACWY Vax®</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabipur®</td>
</tr>
<tr>
<td>Tetanus</td>
<td>*Single preparation no longer available. Combined Adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis preparation given.</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>TicoVac®</td>
</tr>
<tr>
<td>Typhoid (Polysaccharide injection for vaccination)</td>
<td>Typherix®, Typhim Vi®</td>
</tr>
</tbody>
</table>

c) Vaccination scheduling during biologic therapy

Seasonal Influenza vaccine – receive annually
Pneumococcal vaccine – receive once. Check titres every 5-10 years (38).
9. Pathway A

Crohn’s Disease Biologic Pathway

If contraindication to anti-TNF therapy = Vedolizumab 1st Line

Moderately-to-Severe active Crohn’s (TA 187)
Failure or intolerance of immunosuppressant
Adalimumab SC
Infliximab IV

Active Fistulating CD (TA 187)
Infliximab = 1st Line
Consider Adalimumab/Vedo/Ust
(if contraindication to Infliximab)

Assess response at 12-16 weeks = NICE REVIEW

Good Response

Partial Response

Optimise anti-TNF (drug trough + antibody levels + Pathway C
Add/optimize immunosuppressant (if suitable + not already on)

Primary non-response – No clinical response to initial biological therapy

Alternative anti TNF (if neutralising Ab’s) or Vedolizumab (TA 352)
Ustekinumab (TA456)

Assess response (After ~ 8/52)
e.g. repeat drug and antibody levels

Poor response

Alternative anti TNF (if neutralizing Ab’s) or Vedolizumab (TA 352)
Ustekinumab (TA456)

Clinical trial

Surgery

Good Clinical response

Assess response at 12/12 = NICE REVIEW

Reassess response at 12/12 = NICE REVIEW

Remission

Partial/Incomplete response

No response

Consider stopping Biologic + maintaining immunosuppressant

Continue + optimise biologic therapy +/- immunosuppressant
Consider switching therapy

Switch to alternative biologic
Vedolizumab (TA352)
Ustekinumab (TA456)

Remission for biologic cessation is defined as asymptomatic and biochemical and/or endoscopic
and/or radiological evidence of healing
9. Pathway B

**Ulcerative Colitis Biologics Pathway**

**NICE CG 166**

- **Moderately to severe active UC**
  - Anti-TNF (TA 329) Infliximab (IV), Golimumab (s/c), Adalimumab (s/c)
  - Vedolizumab (IV) (TA 342)
  - Assess response by 12/52
  - Poor response
    - Optimise anti-TNF (trough & ab levels) (Pathway C)
    - Add or optimise immunosuppressant
    - Consider a Flexible Sigmoidoscopy
    - Assess response after 8/52
    - Repeat cycle x 2 if needed to optimise
    - Clinical response
      - Repeat cycle x 2 if needed to optimise
    - Remission
      - Consider stopping biologic and maintaining immunosuppressant
    - Partial /Incomplete response
      - Optimise biologic + Immunosuppressant
    - No response = switch therapy
      - Alternative biological Surgery

- **Acute Severe UC**
  - Infliximab (IV) (TAS 163) 5mg/Kg
  - Assess response daily **
  - Poor response
    - Wean steroids commence Azathioprine
    - Colectomy
    - **Consider an extra 5mg/kg IFX if no clinical benefit + extensive haemorrhagic colitis**
  - Clinical response
    - Wean steroids commence Azathioprine
    - Colectomy
  - Partial /Incomplete response
    - Optimise biologic + Immunosuppressant
    - Alternative biological Surgery
  - No response = switch therapy
9. **Pathway C**

**Loss or Poor response to Biologic anti-TNF treatment**

- **Anti-TNF drug trough level**
  - **Undetectable**
    - **Anti-TNF drug antibodies**
      - **Detectable**
        - Drug being neutralised by neutralizing drug Ab’s
        - *Anti-TNF antibody level >10*
          - Consider adding immunosuppressant therapy
          - Consider stopping anti-TNF
          - Switch drug – another anti-TNF Ustekinumab, Vedolizumab
        - *Anti-TNF antibody <10*
          - Add in and/or optimise immunosuppressant
          - Increase dose/frequency of anti-TNF
    - **Undetectable**
      - *Insufficient drug available*
      - *Check adherence*
      - *Accelerated drug consumption/clearance*
      - *Improve adherence*
      - *If adherence is good*
      - - Reduce time between doses or increase drug dose

- **Anti-TNF drug trough level**
  - **Detectable**
    - Anti-TNF drug antibody may be positive or negative
    - Target Infliximab drug trough level = 2-5 ug/ml
    - Target Adalimumab trough level = 5-10 ug/ml
    - Low drug trough + Antibody <40 or undetectable
      - Increase drug dose/frequency
      - Add in immunosuppressant
      - If responsive = continue therapy and review after 6/12 months
      - If partial response = optimise biologic therapy (further Ab + drug level testing) + immunosuppressant if no response = consider entry into a clinical trial/alternative biologic therapy/surgery
    - Low drug trough + Antibody >40
      - Consider a switch to an alternative anti-TNF/biologic
      - Add in immunosuppressant if NOT switching therapy
    - 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, Vedolizumab

**Antibodies** – The precise level of antibody is currently undefined
A low level of antibody can be clinically significant, if the antibody is neutralizing the drug
Antibodies can be reduced by immunosuppressant, or anti-TNF adjustments
An antibody level >40 is unlikely to be cleared by immunosuppressant or anti-TNF adjustments

**Drugs**
- Target Infliximab drug trough level = 2-5 ug/ml
- Target Adalimumab trough level = 5-10 ug/ml

**Pathway**
- Confirm active IBD flare
  - *Faecal Calprotectin*
  - *Bloods (routine: anti-TNF Ab + trough + Endoscopy/radiology*

**Additional Considerations**
- Increase dose/frequency of anti-TNF
- Add in immunosuppressant
- Consider a switch to an alternative anti-TNF/biologic
- Add in immunosuppressant if NOT switching therapy
- Increase drug dose/frequency
- Add in immunosuppressant
- If responsive = continue therapy and review after 6/12 months
- If partial response = optimise biologic therapy (further Ab + drug level testing) + immunosuppressant if no response = consider entry into a clinical trial/alternative biologic therapy/surgery
10. References


