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Alimentary Pharmacology & Therapeutics

Review article: Managing the Adverse Events Caused by Biologics Therapy in Inflammatory Bowel Disease

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To,

Prof Roy Pounder and Dr. Nicholas Kennedy,

Editors,

Alimentary Pharmacology and Therapeutics

Dear Prof Pounder and Dr. Kennedy,

Thank you for your valuable comments on the review article we submitted with reference number APT-1143-2018. We also would like to thank the reviewers.

We have now changed the title of the manuscript as per your suggestion and resubmitted a tracked and clean copy.

The title now reads- Managing the Adverse Events Caused by Anti-TNF Therapy in Inflammatory Bowel Disease

We hope this is to your satisfaction.

Thank you

Yours sincerely

Uday Shivaji, Neeraj Bhala and Prof Subrata Ghosh

Review article: Managing the Adverse Events Caused by Anti-TNF Therapy ~~Biologics Therapy~~ in Inflammatory Bowel Disease

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STRUCTURED SUMMARY

Background

Biological therapy is currently widely used to treat inflammatory bowel disease (IBD). Infliximab, adalimumab and golimumab are currently licensed anti-TNF therapies. Biosimilar anti-TNF monoclonal antibodies are increasingly used. Anti-TNF therapies are most widely used and their adverse effects are best characterised, which may cause significant morbidity and mortality in a small proportion of exposed patients. Gastroenterologists need to understand the mechanism for these effects, recognise these swiftly and manage such events appropriately.

Aim

This review aims to cover the range of potential adverse reactions as a result of biologic therapy and specifically management of these events.

Methods

A Medline and Pubmed search was undertaken. Search terms included were “anti-TNF”, “infliximab” or “adalimumab” or “golimumab” combined with the keywords “ulcerative colitis” or “Crohn’s disease” or “inflammatory bowel disease” and then narrowed to articles containing the keywords “complications”, “side effects” or “adverse events” or “safety profile”. International guidelines were also reviewed where relevant.

Results

Adverse events discussed in this review include infusion reactions, blood disorders and infections (including bacterial, viral, fungal and opportunistic infections) as well as autoimmune, dermatological disorders, cardiac and neurological conditions. Malignancies including solid organ, haematological, and those linked to viral disease are discussed.

Conclusions

Anti-TNF therapy has wide-ranging effects on the immune system resulting in a spectrum of potential adverse events in a small proportion of patients. Research advances are improving understanding, recognition and management of these adverse events.

INTRODUCTION

The use of biologics is currently approved for moderate-to-severe Crohn's disease (CD) and moderate to severe ulcerative colitis (UC)[1-9]. Infliximab, adalimumab and golimumab are antibodies to tumour necrosis factor-α (TNFα). These drugs work on a common pathway of blocking TNFα, a pro-inflammatory cytokine closely linked to acute phase reaction and systemic inflammation, thereby reducing the degree of damage to tissues. These have been developed using different techniques therefore conferring different degrees of immunogenicity. [Infliximab (human-chimeric), adalimumab (fully human), golimumab (fully human), certolizumab (recombinant pegylated humanised Fab' fragment)].

These medications have transformed medical treatment options for inflammatory bowel disease (IBD) in recent years and are prescribed in increasing numbers. As there are less golimumab exposed patients than the other two anti-TNF monoclonal antibodies, less adverse effects have been reported but generally most adverse effects are class effects. Clinicians need to be aware of & recognise adverse events (AE/AEs) that may result from the use of these drugs and also have clear management strategies in different scenarios. This comprehensive review summarises a range of possible AEs providing evidence based guidance where available and pragmatic guidance for areas where evidence is lacking.

AIMS AND METHODS:

A MEDLINE and PUBMED search was undertaken by (U.S, C.L) for articles pertaining to adverse effects of anti-TNF therapy in IBD. After an initial title screen, all relevant articles were examined in full. The main aim of the review is to focus on management of adverse events caused by anti-TNF therapy. For clarity, these AEs are discussed in categories as per systems, alongside recommended course of action including any further investigations or management. Where relevant, this manuscript also refers to international guidelines.

Non-infectious complications and management strategies

Hypersensitivity reactions

Hypersensitivity reactions vary widely in presentation, ranging from acute infusion reactions to delayed hypersensitivity.

- Type I acute hypersensitivity reactions (IgE mediated) present as anaphylaxis
- Type II are cytotoxic; complement-mediated
- Type III are immune-complex related presenting as serum sickness
- Type IV are cell-mediated delayed hypersensitivity; mediated by T lymphocytes

Acute infusion reactions (IR) are defined as those which occur during or within 24 hours of the infusion. The symptoms vary and reactions can range from mild (flushing, dizziness, headache, itching, rash) to severe (anaphylactic-like)[2]. Acute infusion reactions are relatively common, estimated to occur in up to 5% of infusions, with less than 1% of all infusions resulting in a severe reaction[3].

Patients with antibodies to infliximab are at an increased risk of infusion reactions[4] and case reports suggest hypersensitivity to adalimumab are also associated with adalimumab antibodies[5]. A review by the Food and Drug Administration (FDA) reported that injection site reactions were more common with adalimumab[6] with higher reporting odds ratio(ROR) in the 20-29y age group (ROR=16.18). The ROR was seen to reduce with increasing age[6]. Injection site reactions to golimumab in the PURSUIT

study were low at 3.4% with no reported anaphylaxis or delayed hypersensitivity to 6 weeks[7]. Delayed reactions (24 hours to 14 days) presenting with arthralgia, myalgia, fever, fatigue and rash are much rarer (<1%)[3]. The pathophysiology of immunologic features are not completely understood[8].

Management

The management of IRs is generally similar regardless of which agent has caused it. Typically, symptoms improve substantially or resolve completely after infusion rate adjustments and treatment with paracetamol, antihistamines or corticosteroids are provided. Evidence to support the use of premedication with corticosteroids or antihistamines is limited, with patients still experiencing infusion reactions despite pre-medication[9] and therefore should be considered on an individual basis. Injection site pain due to adalimumab can be reduced by using low volume formulations which are free from citrate buffers, with no change in efficacy[10].

In severe acute reactions, it is recommended that infusion is stopped and focus should be on maintaining airway, circulation as per standard anaphylaxis guidelines[11]. (Table 1) Delayed infusion reactions are typically managed by antihistamines, paracetamol and corticosteroids. A systematic review looked at management of infusion reactions and presented useful algorithms to manage mild, moderate and severe reactions[12]. These algorithms are simple, and a pragmatic tool to use for the vast majority of reactions seen in clinical practice[12]. After a hypersensitivity reaction, it is pragmatic to obtain therapeutic drug levels and anti-drug antibody levels.

Table 1- Hypersensitivity reactions to anti-TNF therapy

Complication	Diagnosis	Management Strategy
Type 1 Hypersensitivity This is more common when antibody titres are high. Incidence is higher during re-introduction of drug**s**	• Clinical diagnosis • Serum mast cell tryptase • Detection of antibodies on serum analysis where available	1. Mild reactions: Slow infusion rates 2. Consider hydrocortisone injections as a pre-administration medication 3. Anaphylaxis reactions: Treat as per ALS pathway with adrenaline, steroids and anti-histamines
Type 2 Complement Mediated Non-specific symptoms	• Detection of antibodies on serum analysis where available	1. Symptomatic treatment 2. Consider stopping treatment
Type 3 Immune-Complex Mediated Serum sickness	• Difficult to detect on assays, immune complexes known to adhere to membranes	1. Symptomatic treatment 2. Consider stopping the drug and switch if antibodies are confirmed
Type 4 T-Cell Mediated Delayed hypersensitivity reaction (after 24 hours up to 14 days post-infusion).	• Clinical diagnosis	1. Symptomatic management 2. Consider stopping drug

Anti – TNF: Anti-Tumour Necrosis Factor; ALS: Advanced Life Support

Haematological effects

Leucopoenia

Neutropenia has been reported in anti-TNFα treatment-exposed patients, with up to 20% of patients developing neutropenia on at least one occasion[13]. TNFα up-regulates other pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor, involved in the differentiation and maturation of haematopoietic progenitor cells[14]. TNFα blockade could mediate bone marrow failure by inhibiting stem cell differentiation[15]. However, the reduction in neutrophil count following TNFα inhibitor therapy is not seen for other cells from the same lineage (myeloid progenitor cell), specifically basophils, eosinophils and monocytes. The risk of neutropenia is significantly higher in patients with a low baseline neutrophil count or a previous history of neutropenia[13,16].

Thrombocytopenia

Isolated thrombocytopenia following the use of anti-TNF drugs[17,18] has been reported. There are multiple hypotheses as to the possible aetiology, including autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes triggering the complement cascade, another unknown autoimmune mechanism, or idiosyncratic reaction[18].

Anaemia

Anaemia is considered a marker of active disease in IBD and therefore clinicians need to first consider this as an aetiology. The incidence and prevalence of anaemia was approximately 19% and 28% respectively, in a recent population based cohort study. Crohn's with stricturing disease and long-standing UC were recognised as risk factors[19]. One study showed only marginal improvement in anaemia after treatment with anti-TNF therapy suggesting that disease activity in itself has a major role to play[20].

In this section, anaemia directly attributable to biologics is discussed, which is rare. There are sporadic case reports of aplastic anaemia with infliximab, more commonly in patients with rheumatoid arthritis than IBD[21]. A single case of infliximab induced autoimmune haemolytic anaemia (in a patient found to be anti-nuclear antibody (ANA) positive 1:40) has also been reported[22].

Management of haematological effects

All patients starting anti-TNF therapy should have a baseline complete blood count with repeat testing every three to six months. At the onset of neutropenia, the anti-TNF should be withheld if the neutrophil count is deemed too low by the clinician. The patient should be left drug-free until neutrophil counts recover & anti-TNF therapy restarted when deemed clinically safe. Neutropenia can occur in patients managed with combination therapy with an anti-metabolite and this should be borne in mind and should be discontinued first. A neutrophil count less than 1000/mm^3 should raise concern and <500/mm^3 should lead to discontinuation of incriminating drugs and close monitoring. Rare anti-TNF induced systemic lupus erythematosus should be excluded and sargramostim is rarely necessary after drug discontinuation.

Thrombocytopenia can be managed by drug cessation, corticosteroid therapy or rescue therapy with intravenous immunoglobulin (IVIG). Thrombocytopenia has been reported to be prolonged after cessation of therapy. In severe cases this could persist for up to 6 months and also preclude exposure to any further anti-TNF agents[18]. This is likely to be a class effect and re-challenge with same class could be risky and therefore discouraged[17]. In severe cases, specialist haematology input is suggested.

Anaemia in IBD is more commonly seen due to ongoing disease activity. Clinicians should first consider assessment for disease and strategies to control and manage anaemia secondary to disease as per guidelines. As anaemia related only to therapy is rare, there is no specific guidance in current literature regarding future therapy with anti-TNF. Cessation of therapy would depend on

careful physician-patient discussion taking into account the severity of anaemia and alternative treatment strategies. Involving haematologist in refractory cases would be prudent. (Table 2)

Table 2- Haematological complications with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Leucopenia **Neutropenia**	• Blood count monitoring	1. If < safety threshold: stop drug, monitor blood count 2. Restart drug when counts are within normal range 3. Monitor 4. Consider G-CSF
Thrombocytopenia	• Blood count monitoring • Establish temporal relationship to drug • Secondary cases of low platelets to be excluded including concomitant drug therapy	1. If < safety threshold: stop drug, monitor platelet count 2. Consider IV immunoglobulins & steroids 3. Consider switching to different class of biologic
Anaemia Drug related anaemia is rare but aplastic anaemia can be serious	• Blood count monitoring • Bone marrow aspiration in refractory cases	1. If aplastic anemia: withdraw and stop drug 2. Refractory cases warrant specialist hematology assessment

G-CSF- Granulocyte-Colony Stimulating Factor

Dermatological effects

In addition to skin malignancies anti-TNF therapy can cause a wide range of dermatological conditions. Most notably they include local skin irritation or reaction, increased skin infection rates, psoriasis, eczema, acne, and alopecia. Other rare dermatological complications include erythema nodosum[23], granuloma annulare and interstitial granulomatous dermatitis. Although some of the above complications are also seen as extra-intestinal manifestations of disease, temporal association with biologic therapy should help differentiate disease related complications from drug related complications.

Psoriasis and psoriasiform reactions can occur directly as a result of anti-TNFα therapy, which interestingly is used by dermatologists to treat severe cases of psoriasis. Psoriasis is a relatively common side effect of anti-TNFα therapy, with 1.5-5% of patients developing this manifestation[24]. It is seen most commonly in females, typically 2-6 months following initiation of therapy[25]. A nation-wide cohort study reported incidence rates of anti-TNF induced psoriasis in IBD at 0.5% per patient-year[26]. A more recent study shows a much higher incidence at 10.5%[27], but psoriasiform lesions are more common than psoriasis and have distinctive features. According to current evidence, females, smokers and patients with fistulising disease appear to be at risk[27]. In addition to anti-TNFα induced psoriasis, psoriasiform and drug-induced psoriasiform lesions have been well recognised. Psoriasiform drug reactions can be distinguished histologically from psoriasis and resolve swiftly on cessation of drug therapy. Re-challenge results in recurrence of the lesions. The psoriasiform lesions could be secondary to infections and resolve on its treatment, though the infective origin of these are not always clear nor are their implications[25].

The exact mechanism triggering de novo psoriasis is unclear, although it has been postulated to be secondary to increased cutaneous expression of interferon alpha (IFNα). IFNα is released from dendritic cells to recruit T cells and pro-inflammatory cytokines IL-12 and IL-23. TNFα would

normally block IFNα expression and so anti-TNFα results in up regulation of IFNα[24]. Higher levels of IFN are seen in anti-TNFα induced psoriasis than idiopathic psoriasis[25].

Management

Management of psoriasis due to anti-TNFα depends on severity of symptoms. Milder cases of psoriasis can be treated clinically with topical therapy without cessation of anti-TNF, however more severe cases may require anti-TNFα withdrawal[24]. About 80% of patients respond to a combined approach of steroids and biologics withdrawal[26]. The use of another anti-TNFα agent may result in recurrence of psoriasis in majority of cases (52%)[25]. Ustekinumab has been used in the treatment of CD[28] and psoriasis[29]. There have been rare reports of paradoxical worsening of psoriasis with ustekinumab but not known to cause drug-induced psoriasis[21]. Ustekinumab is potentially an attractive option for treatment of refractory anti-TNFα induced psoriasis[25] requiring withdrawal of primary drug. Methotrexate has been used but does not appear to be effective in all cases[26]. It is a useful option to have in selected cases. (Table 3)

Table 3- Dermatological adverse effects with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Psoriasis Relatively Common (1.5% - 5% of patients on anti-TNFs)	• Clinical diagnosis • Histology of skin lesions • Establish temporal relationship between initiation of biologic therapy and development of psoriasis	1. Specialist involvement from dermatology 2. In mild cases: topical steroid therapy 3. In severe cases: stop drug and consider alternatives such as Methotrexate 4. Ustekinumab for managing both conditions is a viable alternative
Psoriasiform lesions Common	• Clinical Diagnosis • Consider skin infections causing the rash	1. Consider stopping drug in severe cases. 2. Responds well to cessation of drug therapy 3. Treat skin infection as appropriate
Erythema Nodosum **Granuloma Annulare** **Interstitial Granulomatous Dermatitis** Very rare	• Clinical Diagnosis	1. No clear evidence on management as these conditions are rare 2. Specialist dermatology involvement is advised 3. Usually not necessary to withhold or stop drug 4. Clinician decision based on risk: benefit assessment

Anti – TNF : Anti-Tumour Necrosis Factor ;

Autoimmune-like disorders

Autoimmune-like disorders/syndromes are a group of conditions observed in patients on anti-TNF therapy. This was first described in initial studies of infliximab in patients with rheumatoid arthritis[30]. These disorders include a variety of conditions such as positive antibodies e.g. –anti-nuclear antibodies, anti-double stranded DNA antibodies (dsDNA) (commonly IgM type), on immunological testing, various systemic or organ-specific autoimmune diseases as documented in the BIOGEAS registry, drug-induced systemic lupus erythematosus (DIL) called lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optical neuritis & inflammatory ocular disease, multiple sclerosis (MS)-like central nervous system (CNS) demyelination and peripheral neuropathies[31].

William et al described anti-TNFα induced lupus (ATIL) based on the severity of symptoms displayed and suggested that ATIL is a distinct syndrome in itself[32] and are likely to be different from drug induced lupus. In a pooled analysis across various diseases, studies which included patients with IBD showed that whilst ANA positivity was very common after anti-TNF therapy (40%-56%), asymptomatic anti-nuclear antibodies or anti-double stranded DNA antibodies require observation but not discontinuation of anti-TNF. The full range of symptoms of ATIL was seen in only about <1% of patients[32]. Most patients with full blown ATIL had fever, rash, arthritis and haematological abnormalities.

A large case series was reported by Costa et al comparing drug-induced lupus secondary to anti-TNF and classic drug-induced lupus[33]. Both groups had similar systemic features and symptoms but there were some features that distinguished one group from the other. 72% of patients with anti-TNF drug-induced lupus had cutaneous manifestations compared to about 25% in classic drug-induced lupus group. Classic drug-induced lupus was not usually associated with antibodies to dsDNA and extractable nuclear antigen (ENA) or with complement consumption. 90% of anti-TNFα

drug-induced lupus patients were positive for anti-dsDNA antibodies and >50% had anti-extractable nuclear antigen antibodies and decreased serum complement levels[33].

Management

The management of autoimmune-like disorders/syndromes secondary to anti-TNF therapy requires a customised therapeutic approach according to severity of the induced autoimmune disease. ATIL should be considered a distinct condition and managed accordingly. There are features which could help distinguish this. The incidence/prevalence of dsDNA antibodies and hypocomplementaemia is greater in ATIL, whilst anti-histone antibodies, the hallmark of classic drug-induced lupus, are less commonly found[32].

In patients with a positive ANA, it is not in itself an indication for discontinuation of therapy. In the presence of mild features, cessation of therapy is probably sufficient. However, it can be continued in patients with isolated cutaneous lesions or immunological alterations in whom biologics are thought to be essential to treat underlying disease, with closer follow-up. In patients with involvement of internal organs (kidney, lungs, nervous system), cessation of therapy is mandatory with addition of corticosteroids and/or immunosuppressive agents[30,33]. After discontinuation of the incriminating anti-TNF the prognosis is generally very favourable. The presence of diagnosed SLE is a contraindication to anti-TNF exposure.

Cardiac effects

It was reported that worsening cardiac failure was a possible adverse event in a randomised controlled trial investigating the use of anti-TNFα therapy in cardiac failure[34]. Majority of patients enrolled were New York Heart Association III (NYHA) at baseline and the group receiving high dose

infliximab (10 mg/kg) were adversely affected with an increased likelihood of hospitalization, high frequency of worsening heart failure, with the risk of adverse clinical events persisting for up to five months after cessation of therapy[34]. The exact mechanism of heart failure with anti-TNFα use remains unclear.

There have been case reports of second degree and complete heart block after infliximab therapy but are rare[35]. This is more likely to happen in rheumatological conditions as there may be underlying cardiac involvement. A single blind prospective study which included rheumatological conditions concluded that new-onset cardiac arrhythmias, particularly ventricular tachyarrhythmia, developed during infliximab infusion, but their incidence did not achieve statistical significance[36]. Acute coronary syndrome following infusion has been reported but this too is very rare[37]. The rarer cardiac effects are based on reports with a very small number of patients, mostly from the rheumatology cohort who are at higher risk of having cardiac disorders.

Management

Current guidance recommends that use of anti-TNF therapy is best avoided in those with NYHA III/IV heart failure[38]. All patients who develop heart failure while on an anti-TNF agent should discontinue therapy, conventional medication for treatment of heart failure started and specialty advice sought. An alternate class of agent should be considered for the primary disease process. It is still unclear whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYHA class I/II) [38]. For patients commencing anti-TNF therapy who have specific cardiac risk factors such as hypertension, valve disorders or ischemic heart disease, our recommendation is that clinicians should get a baseline electrocardiogram to record QT interval among other features and clinically assess the patient for any features of pre-existing heart failure that may preclude therapy. Not all studies have substantiated an association of anti-TNF therapy with heart failure and this is rare in patients with IBD.

Table 4- Cardiac adverse effects with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Cardiac Failure	• Clinical diagnosis • Objective assessments with investigations	1. Avoid anti-TNFs in NYHA III and IV heart failure 2. If drug precipitates heart failure: stop the drug 3. Treat for heart failure with diuretics and early specialist involvement 4. Switch to another class of drugs
Second and third-degree Heart Block More commonly seen in the treatment of rheumatological conditions; less so with IBD	• 12 Lead ECG • Cardiac monitoring	1. Monitor patients for features of decompensation 2. Specialist involvement for further management 3. Stop drug and switch to another class
Arrhythmias More commonly seen in the treatment of rheumatological conditions; less so with IBD	• 12 Lead ECG • Cardiac monitoring	1. Usually transient and does not need any specific management 2. If transient episodes are self-limiting: consider continuing drug 3. If persistent: seek specialist cardiology opinion

Anti – TNF : Anti-Tumour Necrosis Factor NYHA-New York Heart Association

Neurological effects

Demyelination

Demyelination has been recognised as a complication of anti-TNF therapy. A review of FDA adverse event recording system showed that among 772 reports of neurological complications, 18% of patients had IBD. About 36% of patients had received infliximab and peripheral neuropathy was the most commonly reported event[39]. Demyelination can occur in central or peripheral nervous systems[40]. It is unclear as to whether the relationship is truly causal, or whether anti-TNF triggers an existing tendency for demyelination.

Management

The patients who have a family history of demyelination disorders may be at higher risk and this should be considered before the therapeutic agent is chosen[41]. It is standard guidance to avoid anti-TNF therapy in patients with concomitant multiple sclerosis or history of optic neuritis. In patients who develop neurological deterioration and suspected demyelination during therapy, treatment with biologic agent should be discontinued[41] and specialist neurology opinion should be sought. The clear relationship between demyelinating events and anti-TNF can be difficult to establish as IBD may also be associated with demyelination. Treatment with corticosteroids, IVIG and plasmapheresis are rarely necessary. (Table 5)

Table 5- Neurological reactions with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Demyelination Known to worsen demyelination in patients with multiple sclerosis	• Clinical diagnosis • Nerve Conduction Studies • MRI	1. Stop drug and consider alternatives 2. Seek specialist Neurology involvement 3. Consider pulse therapy with high dose methylprednisolone 4. Consider IV Immunoglobulin

MRI-Magnetic resonance imaging

Infections and management strategies

Biologics are strong immunosuppressive agents and can increase risk of infection depending on their mechanism of action. TNFα is essential for activation, differentiation and recruitment of several immunological cell types; it has a role in granuloma formation, maintenance of granuloma integrity[42] and host response to mycobacteria and intracellular organisms[43]. A recent meta-analysis found that anti-TNF therapy was associated with a greater infection risk than placebo in treating UC but anti-integrin therapy was not; neither class showed an increased infection risk over placebo in CD[44]. Other studies have confirmed increased risk in both forms of IBD.

A recent systematic review by Wheat et al concluded that at present there is no evidence of a higher odds of serious infection from the newly available biologic therapies such as vedolizumab and ustekinumab compared to anti-TNFs[45]. Feagan et al report that infections in patients exposed to ustekinumab for CD is no higher than placebo in UNITI trials[46] and Wils et al reported 1 serious pulmonary infection in a cohort of 122 ustekinumab patients, followed up over 2 years[47]. Bye et al reported an increased risk of Clostridium difficile infection with vedolizumab therapy but concomitant steroid and narcotic analgesics were identified as risk factors[48].

Bacterial infections

Patients receiving anti-TNF therapy have been reported to acquire both common and uncommon bacterial infections. Common sites for infection include upper and lower respiratory tracts, skin and subcutaneous tissue, urinary tract and GI tract[49].

Management

Common infections are treated with oral antibiotics as per local guidelines. A pragmatic approach would be to have a lower threshold to start treatment and switch to intravenous drugs in the presence of systemic symptoms. In severe sepsis requiring prolonged antimicrobial treatment, anti-TNF

therapy may have to be withheld. Restarting therapy can be considered once patients are afebrile, white cell counts within normal range and relevant imaging (CT, MRI pelvis) show no evidence of infective source. (Table 6)

Uncommon infections

Several non-mycobacterial intracellular infections, including listeriosis caused by *Listeria monocytogenes* and legionnaires' disease most often caused by *Legionella pneumophilia* , have been associated with anti-TNF therapy[50]. Listeria sepsis and meningitis has been described in patients receiving anti-TNF drugs[51] and in 2011, the FDA added a boxed warning about the risk of listeriosis and legionnaires' disease for the entire class of TNFα inhibitors[52]. There are a few case reports of listeriosis complicating anti-TNF therapy. Listeriosis carries significant mortality, therefore requiring prompt diagnosis and aggressive treatment. The risk appears to be higher during the first year of therapy[53]. Anti-TNF should be discontinued till the patient recovers from listeriosis.

Management

Suspicion of infection requires confirmatory testing and treatment using standard antibiotic regimes depending on pathogen isolated. Listeriosis is more likely to be seen in patients consuming mould-ripened cheese regardless of whether it is from pasteurised or unpasteurised milk and also from cold smoked gravad fish[54]. In one study from USA, unpasteurised milk and dairy products were noted to significantly increase the risk of infections caused by *E-coli, Salmonella and Campylobacter*[55]. In view of this overall increased risk of infections, it is safer for patients to avoid consumption of unpasteurised milk whilst on anti-TNF drugs.

Mycobacteria and tuberculosis

Tuberculosis (TB) caused by mycobacterium bacilli is a serious infection which carries significant morbidity. TNFα is necessary for a Th1-based cell-mediated immune response important in

activating macrophages to kill intracellular mycobacteria, and limit spread by formation of granulomas[56,57]. The majority of exposed immunocompetent hosts have latent TB (LTB) which can subsequently lead to reactivation of infection if there is compromise to the immune system, such as initiation of anti-TNF drugs[58]. It is therefore critical to identify and treat LTB prior to starting anti-TNF therapy[58].

An association between anti-TNF therapy and development of TB was noted when the FDA MedWatch spontaneous reporting system demonstrated 70 TB cases in a median of 12 weeks after initial infliximab exposure, in 2001[59-68]. Both extra-pulmonary and disseminated TB are more common in patients treated with anti-TNF therapy, compared with immunocompetent patients[59-60]. It has been hypothesised that the early occurrence of TB after infliximab may suggest reactivation of LTB rather than a de novo infection[60]. Due to the high risk of reactivation, screening for TB is recommended prior to starting anti-TNFα.

The diagnosis of LTB can be difficult and should include a combination of detailed history and supportive investigations. At present, IGRA (interferon gamma release assay) and TST (tuberculin skin test) are commonly used in most centres. In a study by Mariette et al which looked at how effective the available tests are, it was noted that when one of the IGRA tests replaced TST, it influenced the decision made by physicians, leading to 28% fewer patients receiving anti-TB (ATB) prophylaxis[61]. This is likely because IGRA tests are more specific. As per this study, IGRA does not appear to be affected by corticosteroid or immunosuppressant therapy[61]. However, this may not always be the case as shown in an ex vivo study in which corticosteroids and infliximab reduced the performance of IGRA[62]. At present, IGRA is possibly more reliable than the other options available. TST is less specific and can be less frequently positive due to corticosteroid or immunosuppressant therapy and this should be borne in mind. Based on their findings, Mariette et al proposed the an algorithm for assessing patient, which is now generally applied prior to starting anti-TNFα therapy[61]. All patients should undergo appropriate history +/- chest x-ray. For those with a positive history or

x-ray, treat with ATB prophylaxis. For those with negative history, check with IGRA test (authors recommend GOLD, followed by T-SPOT if indeterminate). Those with negative results require no further screening. Those with positive results require ATB prophylaxis. Patients with indeterminate GOLD and T-SPOT test should undergo TST testing. Negative results require no further action, but a positive TST should be treated with prophylaxis[61].

In patients who have a positive TST and negative IGRA, the degree of clinical suspicion should guide management, based on history and chest x-ray with a very low threshold to treat the patient. Generally, performing both TST and IGRA is not recommended. An initial indeterminate borderline IGRA can be followed up with TST and if the latter is positive the patient should be treated. The CDC recommend testing with either IGRA or TST, but a combination of both may be appropriate where clinical suspicion of LTB is high, or risk of subsequent LTB reactivation may result in a poorer outcome (such as those on immunosuppressants)[63].

Management

Guidelines by European Crohn's and Colitis organisation (ECCO)[26] and British Thoracic Society (BTS)[58] on screening and management of TB are similar in principle, suggesting treatment of LTB prior to initiation of anti-TNF therapy with a complete therapeutic regimen. If there is clinical suspicion +/- radiographic changes suggestive of TB, patients should be referred for treatment of LTB[58]. Other patients should undergo LTB screening tests. The optimal screening strategy for these patients is still debatable.

After diagnosis of latent TB in a patient with IBD, appropriate treatment should be administered for at least 3 weeks prior to commencement of anti-TNF therapy[64,65] ; however if treatment with anti-TNF therapy is considered very urgent simultaneous treatment for latent TB and IBD may be considered. Alternative therapies such as vedolizumab or ustekinumab may also be considered for UC or CD. Short latent TB therapies are increasingly considered such as rifampicin for 4 months or isoniazid plus rifampicin for 3 months as adherence to 9 months of daily isoniazid poses

challenges[66,67]. Exposure to active TB during anti-TNF therapy should lead to prompt re-evaluation for latent or active TB. In case of active TB, anti-TNF should be discontinued and active TB treated. If absolutely necessary, anti-TNF may be resumed after at least 2 months of anti-TB therapy with satisfactory response, though it may sometimes be resumed earlier if absolutely necessary. Increasingly other monoclonal antibodies such as ustekinumab or vedolizumab are being considered. Annual re-testing for LTB in patients on anti-TNF therapy depends on risk factors for exposure to TB and desirable in geographical areas with endemic TB. (Table 6)

Table 6- Bacterial infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Common bacterial infections		
Respiratory Tract **Urinary Tract** **Gastrointestinal** **Cellulitis**	• Clinical diagnosis • Relevant investigations depending on symptoms	1. Appropriate antibiotics based on site of infection 2. Consider early therapy 3. If any signs of sepsis: stop drug 4. Restart biologics when good evidence of resolved infection. (WCC, imaging)
Serious Bacterial Infections:		
Listeriosis **Legionnaires' disease** **Septic Arthritis** **Septicemia**	• Serology • CT/MRI of brain • Lumbar puncture if meningitis suspected	1. Appropriate antibiotics based on sensitivity 2. Seek specialist microbiology advice
Tuberculosis (TB):		
Latent TB Re-Activation	• Risk assessment based on initial screening with Quantiferon or T-Spot Testing • Thorough history and risk factor assessment • Chest X-Ray	1. If positive or indeterminate: involve specialists 2. Treat as per ECCO guidelines and British Thoracic Society Guidelines 3. Risk: Benefit analysis by clinician 4. Consider alternative therapy i.e. vedolizumab or ustekinumab

WCC-white cell count

Viral infections

A majority of human viral infections are self-limiting but some are capable of causing chronic infection [e.g. human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)]. There are viruses linked to malignancy, such as Epstein-Barr virus (EBV) and human papilloma virus (HPV). EBV will be discussed in more detail in 'malignancy' section of this text.

Varicella (VZV) and Shingles

This can present with severe or disseminated disease if contracted while on anti-TNF therapy[68]. In one study, the prevalence of prior varicella zoster virus (VZV) infection among IBD patients was greater than 90%[69] and it was not noted that a significant number had a VZV IgG negative status. It is known that patients with IBD are at a higher risk of VZV infection and more so when on immunosuppressive therapy[7071].

Herpes zoster or shingles is caused by reactivation of VZV. The incidence of shingles is again increased in patients with IBD, the elderly population at particular risk. In a study looking at herpes zoster in IBD, it was seen that patients with CD were at higher risk; age >45 years, treatment with corticosteroids for >2 weeks, thiopurine therapy were associated with increased risk of infection[72]. Long et al reported similar findings and also noted that patients on anti-TNF therapy for IBD are at higher risk of herpes zoster with an odds ratio of 1.81 (95% CI: 1.48-2.21)[73].

Management

Immunocompromised patients exposed to VZV should be treated with VZV immunoglobulin[74]. Patients who contract VZV or shingles during a period of immunosuppression require antiviral therapy. If oral therapy is appropriate, valganciclovir should be considered as this provides higher oral bioavailability than aciclovir[75]. (Table 7)

Prevention of infection is possible due to availability of effective vaccines. It is recommended that all patients are screened for evidence of past infection prior to starting biologics or immunosuppressives including steroids. ECCO suggest that in seronegative patients two-dose course of varicella vaccine should be given at least 3 weeks prior to commencement of therapy[65]. If subsequent immunisation is necessary, it can be administered after a 3–6 month cessation of all immunosuppressives as both the VZV and shingles vaccines are live vaccines[75], although there is emerging evidence that administration of live zoster vaccine to patients already on anti-TNF therapy did not result in disease and there was expected immune response to the vaccine[73].

Hepatitis B

TNFα and interferon (IFN)γ are released by cytotoxic T lymphocytes on antigen recognition of the hepatitis B virus, activating two viricidal pathways, plus antigen non-specific T cells & macrophages[76]. Reactivation of HBV may occur during anti-TNF therapy, or on subsequent withdrawal (secondary to immune reconstitution). Reactivation of chronic HBV carriers (hepatitis B surface antigen (HBsAg) positive, undetectable HBV DNA, normal LFTs) after anti-TNF therapy has been reported[77]. Patients who have had HBsAg seroconversion following exposure to HBV [HBsAg negative, anti-HBc (core antibody) positive and anti-HBsAg antibody positive] have been successfully treated with anti-TNF therapy without HBV reactivation during follow up[78]. Chronic active HBV patients already successfully controlled with antiviral therapy prior to introduction of anti-TNF show no deterioration in the viral load or liver enzymes[79,80]. A comprehensive review by Pattullo[81] looked at incidence & prevalence of HBV reactivation in IBD when treated with immunosuppressants without HBV prophylaxis; risk stratification of patients was also done based on type of biologic therapy[81]. The incidence of immunosuppression related HBV reactivation was noted to be about 36% in HBsAg positive patients. The overall prevalence of HBV in IBD ranged from 0.6-17% for HBsAg positive patients, and 1.6-42% for HBsAg negative/anti-HBc positive

patients. The risk estimate of HBV reactivation was reported to be moderate (1-10%) with anti-TNF[81].

Management

All patients should be screened prior to initiation of therapy, although which patients should receive antiviral therapy remains unclear. Screening should be carried out checking for hepatitis B surface antigen, antibody to surface antigen & anti HB core antibody levels and if HBsAg or anti-HBc is positive, DNA quantification should be done[65]. Chronic HBV carriers and those with HbsAg seroconversion should be considered for antiviral therapy and hepatology involvement. It is recommended that patients who are due to start biologics (moderate risk) are given anti-viral prophylaxis if they are HBsAg positive and continued for at least 6 months after completion of immunosuppressive therapy[81]. In case of reactivation, it is recommended that one of the antivirals is started and continued for at least 6 to 12 months after immunosuppressive therapy has been stopped. The antiviral medication of choice may depend on the patient's individual circumstances, and the planned duration of immunosupression[82]. Entecavir and tenofovir are now preferred anti-virals in IBD patients due to their rapid onset of action, highest anti-viral potency with low incidence of resistance[65]. Whilst lamivudine is used, this has its limitations if long term therapy is required, as resistance can occur in up to 30% of patients after 1 year and 70% after 5 years[82]. Peginterferon-alpha-2a (IFNα) is best avoided due to the risk of myelosuppression and also risk of exacerbating CD[65].

Hepatitis C

TNFα appears to be involved in the pathogenesis of HCV, with patients with higher serum TNFα levels less likely to respond to anti-viral therapy[83]. TNFα blockade may increase reactivity of peripheral T cells to antigen stimulation[83]. Biologics have an acceptable safety profile for use in

patients with HCV and is not contraindicated in concomitant HCV infection. However, in the presence of acute HCV, anti-TNF therapy is contraindicated[84]. In the presence of chronic HCV, the decision to treat with anti-TNF depends on liver synthetic function. It is best avoided in patients who are Child-Pugh category B or C[84]. HCV patients being treated with anti-TNF therapy should have close monitoring of aminotransferases with consideration for discontinuation of treatment with continued elevations[83]. The guidelines from ECCO suggest cautious use of antivirals due to drug interactions[65]. Infection diagnosed whilst on anti-TNF therapy does not necessarily require cessation of therapy[65]. There is no data yet on the use of newer antivirals for HCV in the context of biologics use for IBD but there are no contraindications for their concurrent use.

Management

The ECCO guidelines are equivocal about screening for HCV prior to use of immunosuppressive therapy[65]. However, it would be prudent to screen patients who are likely to need biologics considering the high curative rates with newer anti-viral drugs for HCV. All patients with HCV infection should be discussed and managed jointly with hepatology services, especially when biologics are indicated for IBD. During the course of therapy, close monitoring of liver functions is key.

HIV infection

The interaction between TNFα and the human immunodeficiency virus (HIV) has been the subject of much scrutiny. The molecular pathway by which HIV expression is upregulated by TNFα is well described[85,86]. Despite these findings, use of anti-TNF in HIV-patients must be balanced with a potential increase in the risk of opportunistic infections in patients with an attenuated immune system.

The evidence base for advice regarding use of biologics in patients with HIV and IBD is limited. Within a cohort study and several case reports, biologic therapy with infliximab in refractory IBD

patients has been demonstrated to be effective in inducing disease remission with only a minority experiencing adverse effects[87-77]. It is important to note that initial CD4+ count in patients included in these studies are > 200 cells/mL. The ECCO guidelines[65] also suggest that the HIV-IBD cohort of patients are less predisposed to infection on highly active anti-retroviral therapy (HAART) than if they did not receive HAART. In this cohort, adverse effects have presented as either a pre-disposition to infections, deranged CD4+ count or HIV viral loads.

Abreu et al describe an HIV positive, thiopurine-intolerant patient treated with IFX for a UC-flare unresponsive to steroids[88] who had been on ART (emtricitabine/tenofovir/efavirenz) with undetectable HIV viral load & CD4+ count of 357/mmc prior to infliximab therapy. Although excellent disease response was achieved, he was diagnosed with listeriosis and was successfully treated. (CD4+ count 350/mmc). Infliximab was restarted with no clinical consequences. It is likely these patients with IBD remain at increased risk of opportunistic infections[89].

Other examples of adverse effects of biologics in HIV are reported in the rheumatology cohort[90]. In one case series[91], a patient who was not on HAART therapy was observed to have an increase in viral load (22,148 c/ml to 428,503 c/ml) following initiation of infliximab therapy. This required temporary cessation of infliximab and the rise was not observed at re-administration.

Within the limited evidence available, it is noted that patients do benefit from adequate disease response with no specific HIV-related complications. Due to risk of AEs, it is recommended that screening for HIV is undertaken prior to treatment with biologics and patients with IBD recognised as HIV positive are managed by a multi-specialty team. Generally, in the absence of other infections treatment of HIV infected patients with anti-TNF is relatively safe. This group of patients must ideally be on HAART. A discussion about potential increased risk of infection, baseline blood tests including CD4+ count (ideally 200 cells/mL+), and HIV viral load is necessary. Close monitoring throughout duration of therapy is key. An Increase in HIV viral load needs discussion with specialists and discontinuation of biologic may become necessary. Any overt sign of infection merits hospital

admission to identify and treat the infection source and biologics paused. Restarting biologics should be discussed based on clinical aspects of each case. (Table 7)

Table 7- Viral infections in the use of anti-TNF therapy

Complication	Diagnosis	Management Strategy
Varicella Relatively common	• Clinical diagnosis • Serology testing available	1. Treat with varicella immunoglobulin 2. Antimicrobial therapy with valganciclovir
Chronic Stable HBV Reactivation of chronic infection	• Screening for HBV mandatory • Close monitoring of liver function and viral load	1. Joint care with Hepatologist 2. May require treatment with antivirals 3. Biologics can be continued unless acute fulminant liver failure suspected
Chronic Active HBV on antiviral therapy	• Screening for HBV mandatory • Close monitoring of liver function and viral load	1. Continue antivirals 2. Entecavir and tenofovir drugs of choice
Hepatitis C	• Screening for HCV recommended prior to anti-TNF therapy • Close monitoring of LFTs and HCV RNA Load in HCV infected patients	1. Joint care with Hepatologist 2. Continue biologic with close monitoring 3. No contraindication for therapy
Cytomegalovirus (CMV)	• Check serology for CMV IgM and viral PCR • Supported by tissue diagnosis with histology and immunohistochemistry	1. Treatment with IV ganciclovir and switch to oral valganciclovir for total of 2-3 weeks 2. Use foscarnet as per sensitivities 3. If systemic CMV infection: consider stopping anti-TNF
Human Immunodeficiency Virus	• Close monitoring in addition to CD4+ counts	1. Continue biologics when HAART established and CD4+ counts are above 350 2. Consider withholding biologic when CD4+ <200 3. Joint care with multidisciplinary decision approach

Anti – TNF : Anti-Tumour Necrosis Factor ; HBV-Hepatitis B virus; HCV-Hepatitis C virus; LFTs- liver function tests; PCR- polymerase chain reaction; HAART- highly active antiretroviral therapy

Fungal infections

Patients with IBD are known to be at an increased risk of fungal infections. This is due to multiple factors such as severity of disease activity, comorbidities, treatment with opioids, surgery, poor nutritional status, leucopenia and older age[92]. Another factor is immunosuppressive therapy, important of which are anti-TNFs. A risk factor analysis by one recent systematic review reported anti-TNF therapy as the predominant factor associated with fungal infections[92].

Aspergillosis

Aspergillosis, caused by *Aspergillus fumigatus* is a serious pulmonary infection which warrants prompt diagnosis and treatment. Attenuation of the inflammatory pathway through TNFα blockade alters the cytotoxic immune response to fungal infections and in aspergillosis, it is involved in polymorphonuclear leucocyte activation in response to infection[93]. The evidence is mostly from case reports. In 2001, a case of invasive pulmonary aspergillosis was reported in a patient with CD on anti-TNF therapy[94]. There have been other case reports since but overall, it appears to be a rare occurrence. This usually presents initially with a poorly productive cough and can progress to respiratory insufficiency; radiological changes are seen[94-95].

Management

The definitive diagnosis is on culture of broncho-alveolar fluid. The infection is treated with prolonged anti-fungal therapy based on sensitivities; amphotericin B or voriconazole or caspofungin is used. The condition carries very poor prognosis. Concomitant tuberculous cavity needs exclusion. (Table 8)

Histoplasmosis

This is another potential opportunistic infection reported in patients exposed to anti-TNF treatment. In a case series of ten immunocompromised subjects from an area endemic with histoplasmosis, 9

contracted histoplasmosis shortly after commencing infliximab infusions. Clinical presentation can be varied and include pulmonary, extra-pulmonary or disseminated disease symptoms which are non-specific[96].

Table 8- Fungal infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Candidiasis Commonly localised infections but systemic and invasive infection can be life threatening	• Serology, culture and molecular studies	1. Localised infections: Topical therapy 2. Invasive infections: i. Stop biologic ii. IV Fluconazole iii. Seek specialist advice
Aspergillosis Pulmonary symptoms and invasive infection	• Serology, culture and imaging	1. Stop biologics 2. IV Anti-fungal therapy (Consider IV voriconazole) 3. Caspofungin is another option 4. Specialist involvement
Histoplasmosis Usually pulmonary infection	• Serology, culture and radiology	1. Stop biologic therapy 2. Treatment with either one of: i. Amphotericin B initially and step-down therapy to an azole preparation ii. Itraconazole
Pneumocystis Jirovecci	• Clinical diagnosis • Culture, microscopic and molecular diagnosis	1. Co-trimoxazole 960mg BD, if severe infection increases to 1.44 g BD 2. Specialist involvement

Management

Invasive fungal infections should be treated with systemic antifungals and all immunosuppressant medication should be reviewed. The FDA in 2008 have issued post market drug safety information alerting healthcare providers that invasive fungal infections and histoplasmosis in patients receiving anti-TNF drugs are not being swiftly recognised, resulting in possible delays to patient therapy. The FDA recommends the involvement of infectious diseases specialists[97] in the management of such cases. (Table 8)

Other Opportunistic infections

Cytomegalovirus (CMV)

CMV infection (detected by serology) could be due to reactivation of latent infection during immunomodulator or biologic therapy, but usually is itself mild or asymptomatic even on immunosuppressants. However, CMV colitis, retinitis, pneumonia or severe CMV infection during treatment of IBD requires further assessment[75] to plan management. Nevertheless, not all cases of CMV infection in anti-TNF use progress to CMV disease[98].

The diagnosis of CMV disease using histopathology with immunohistochemistry is highly sensitive and specific. This combined with CMV viral load (CMV DNA detected by PCR in serum & tissues) can provide most information about disease state[75]. CMV viral loads of >250 copies/mg is a predictor for patients presenting with corticosteroid-resistant disease[75].

CMV disease manifesting as colitis is a recognised complication of IBD and should be screened for in those patients presenting with acute severe colitis[99]. Typically, patients may have had previous exposure to immunosuppressive therapy and experienced prolonged corticosteroid therapy or corticosteroid-refractory disease. CMV can also be a cause of chronic pouchitis[100].

Management

It is important that diagnosis is established swiftly. When considered as a differential diagnosis, testing for CMV viral load with PCR is recommended to look for CMV disease especially in ill patients with systemic manifestations. Histology and immunohistochemistry may be used to support the diagnosis of CMV colitis. Once diagnosed, ECCO recommend a 2-3 week course of ganciclovir therapy for CMV disease, and immunosuppressants are withheld[75]. However, a retrospective cohort case study of CMV-positive colitides, identified that patients with milder colitis were less likely to be treated, and could respond to standard immunosuppressive therapy without additional treatment for

CMV. CMV may be transiently reactivated and disappear without antiviral therapy. In one study it was noted that those with more severe disease were more likely to be treated with ganciclovir, and were more likely to require either rescue therapy or surgery, despite adequate treatment of CMV[101]. CMV colitis complicating UC leading to acute severe colitis can be challenging to manage. A study by Kopylov et al reported that the outcomes for patients with severe colitis. Patients received infliximab/ciclosporin with ganciclovir vs ganciclovir alone, and they had similar colectomy rates[102]. In patients who test positive for CMV whilst on anti-TNF therapy, there is a evidence that anti-TNF can be continued[103]. (Table 7)

Pneumocystis pneumonia (PCP) or pneumocystis jirovecci pneumonia (PJP)

This is a serious infection reported in patients after use of immunosuppressants. A large population based cohort study looked at risk of PJP in IBD patients[104]. Although there is some evidence that the overall hazard risk of PJP in IBD is higher than normal population, the absolute risk of PJP is considered to be very low (0.03% in their cohort)[104]. In a large case series of PJP after infliximab use, mean onset of symptoms reported was 21 days although majority of patients were exposed to concomitant immunosuppressive therapy. Over a quarter (27%) of patients died[105] in these reported series, so early recognition and therapy is paramount. ECCO guidance recommends that patients on triple immunotherapy with one being a calcineurin inhibitor or anti-TNF should receive standard prophylaxis with Trimethoprim-sulfamethoxazole (co-trimoxazole) if tolerated. It should be considered in those on dual immunosuppression especially if one is a calcineurin inhibitor[75] and in anti-TNF regimens with associated corticosteroid use[75]. However, pill-burden and side effects are to be kept in mind. Co-trimoxazole is an effective option for prophylaxis and active infection. Clinicians should discuss with their local microbiology and infectious disease departments. Although more recent studies report very low risk, clinicians have to be vigilant throughout the course of treatment and decision on prophylaxis has to be on a case-by-case basis. (Table 8)

Infection prevention and vaccination recommendations

The main focus of the article is on management of adverse effects and our stress on prevention though very important, is limited as these have been extensively addressed in ECCO guidelines. ECCO guidance recommends that prior to immunosuppression a detailed history and examination including prior bacterial, viral and fungal infections, particularly herpes, VZV, TB exposure, prolonged travel/stay or plans to travel to TB endemic or tropical areas and completion of childhood vaccination programmes. Further advice should include cervical smear screening for women, food hygiene and avoidance of raw and unpasteurised foods. Education on safe use and preparation of dairy & meat products can benefit patients at risk of Listeria infection whilst on anti-TNFα therapy. Live attenuated vaccines must be avoided on immunomodulator or anti-TNF therapy and ideally patients should receive annual inactivated influenza vaccine and pneumococcal vaccine as required. Prior to the onset of immunosuppression, consider vaccination with any outstanding routine vaccines plus HBV, VZV (if seronegative and no clinical history) and HPV[75]. If patients require live vaccines during therapy, the risk: benefit assessment of vaccination should be undertaken. Patients are usually immunocompetent within 3-12 months[106] after cessation of therapy. Corticosteroid therapy alone is not considered to cause significant immunocompromise unless high doses (20mg or higher) have been used continuously for more than two weeks[106].

Malignancy

Malignancies thought to be linked to immunosuppressive agents and anti-TNF use include solid organ malignancies, non-melanoma skin cancer (NMSC), melanoma, lymphoproliferative malignancies, and those with viral association such as EBV-related lymphomas and HPV-related cervical cancers or dysplasia. However, difficulty remains in establishing a cause-effect relationship.

A possible association between anti-TNF use and malignancy first arose from post-marketing reports to the FDA. There were 26 cases of lymphoma reported in patients with rheumatoid arthritis or CD disease treated with etanercept or infliximab[107]. Further studies demonstrated an increased risk for solid organ and NMSC in patients treated with anti-TNF and further immunosuppressive therapies[108]. Many IBD patients are either on multidrug regimes or have had past exposure to thiopurines (or other immunosuppressants) prior to anti-TNF usage.

Historically most trial data is from the rheumatology population. A meta-analysis derived from nine clinical trials of patients receiving anti-TNF treatment or placebo identified a number needed to harm of 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months[109]. The malignancy rates were significantly more common in those treated with higher doses (≥6mg/kg of infliximab every 8 weeks or 40mg of adalimumab alternate weeks)[109]. A more recent meta-analysis of 74 randomised controlled trials concerning adalimumab and infliximab showed no overall relative risk (RR) increase on short term follow up for malignancy with the exception of NMSC which had a RR of 2.02 (95% CI 1.11-3.95)[110]. A 6-year follow up study from the national Danish registers only identified three solid organ malignancies and one case of melanoma, with total follow up ranging from 0.1-72.1 months[111]. The Crohn's therapy, resource, evaluation and assessment tool (TREAT) registry is collecting prospective data on large number of CD patients to evaluate the long-term safety of CD therapies. Data published from the registry in 2006 showed mortality rates to be similar

between infliximab and non-infliximab patient groups after a short period of follow up (mean follow up 1.9 years)[112]. Subsequent data from the registry published in 2014 (with follow up of up to 7.6 years) has shown that none of immunosuppressants, infliximab or combination therapy to be an independent risk factor for malignancy[113]. However, the follow-up period remains short and future analysis of the registry is likely to provide further evidence.

The CESAME Study Group[114] assessed the impact of thiopurine use on development of NMSC–comprised of basal cell carcinoma, squamous cell carcinoma and lymphoproliferative disorders (increased risk found in the thiopurine group). Although a large number of patients were included, the risk of malignancy secondary to biologics could not be assessed due to relatively small number of patients on these drugs[115]. A study by Long et al published in 2010 assessed risk of malignancy and concluded that IBD in itself increased risk of NMSC (incidence rate ratio IRR 1.64 95% CI 1.51-1.78) and a nested case-control model showed an increased risk because of recent biologic use among patients with CD (adjusted OR 2.07, 95% CI 1.28–3.33)[116]; patients on combination therapy had the highest OR compared to medication-free patients (OR 5.85 95%CI 3.2-10.8)[116]. Another study in 2012 reported that patients were at higher risk of melanoma when exposed to biologics and NMSCs were mainly related to thiopurine therapy[117]. The most recent French national cohort study showed an increased risk of lymphoma in treatment exposed patients. When compared with unexposed patients, the risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR, 2.60; 95% CI, 1.96-3.44; P <0.001), anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60-3.64; P < 0.001), or combination therapy (aHR, 6.11; 95% CI, 3.46-10.8; P < 0.001)[118].

There remains concern about cases of hepatosplenic T-cell lymphoma (HSTCL) (a rare and aggressive form of non-Hodgkin's lymphoma affecting predominantly young men) occurring following infliximab, adalimumab or thiopurine use. In a study published by Thai et al, they reported 22 cases of HSTCL in IBD and most were associated with thiopurine therapy either as monotherapy or in combination with anti-TNF. Whilst a link is recognised, quantifying this risk to individual patients

on current evidence is difficult[119].They also concluded that despite the risk, benefits of treatment far outweighed the risks[120].

Secondly, observational studies have noted a potential predisposition to development of EBV related lymphoproliferative disorders in IBD patients, in particular those treated with thiopurines and anti-TNFα agents[75]. Patients with EBV are predisposed to post-transplant lymphoproliferative disorders (PTLD), where T-cell immune surveillance is impaired[75]. EBV related lymphomas may present in the gut, rather than nodal sites. Screening for EBV should ideally be considered, however there is no current vaccination for EBV naïve patients. In those developing EBV on therapy, treatment with antiviral medication and withdrawal of therapy should be considered[75]. IBD itself does not appear to increase risk of lymphoma diagnosis[121]. However use of a thiopurine for IBD or combination therapy with an anti-TNFα may increase risk[121]. Establishing any isolated effect of anti-TNFα on lymphoma development is challenging. In a meta-analysis looking at lymphoma rates in CD patients treated with anti-TNFα, two thirds of all patients were also receiving immunomodulator therapies[122] ; anti-TNFα treated patients appeared to have an increased risk of lymphoma (SIR 3.23 95% CI 1.5-6.9) compared to the expected population rate[122]. The SIR was also increased when compared to previously studied patients on immunomodulator therapy alone (1.7 95% CI 0.5-7.1), however this did not reach statistical significance[122]. There were too few patients treated with isolated anti-TNF therapy to determine the individual risk of anti-TNF usage on lymphoma development[122].

Management principles in malignancy

The association between various malignancies and anti-TNF treatment remains unclear, but it is important that patients' history of previous or pre-existing cancer is carefully documented prior to initiation of biologic treatment. The use of biologics as monotherapy can be considered in patients with previous history of cancer. Axelrad et al noted that at 5 years after prior cancer diagnosis no significant difference in cancer free survival could be demonstrated between IBD treatment with anti-

TNF monotherapy, immunosuppressant monotherapy, anti-TNF combined with thiopurine therapy, though numerically anti-TNF monotherapy had the least cancer recurrence[123]. In a meta-analysis of 16 studies of immune mediated diseases, including 8 studies involving IBD patients, similar rates of cancer recurrence were observed among individuals affected by previous cancer who received no immunosuppressives, anti-TNF monotherapy, immunosuppressant therapy or combination therapies[124]. Therefore, in patients with a history of cancer, recent or past, effective therapy for IBD can be used after consideration of risks & benefits and discussion with oncologists. ECCO guidelines also provide advice on managing IBD patients with previous history of malignancy[125]. Generally, among biologics, monotherapy anti-TNFα, vedolizumab or ustekinumab may all be used, but often thiopurines are avoided.

Table 9- Malignancies with anti-TNF therapy

Complication	Causative drug/s	Diagnosis	Management Strategy
Melanoma	Anti-TNF	• Clinical diagnosis • Skin biopsy	1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Non-melanoma skin cancer	Dual Anti-TNF + thiopurine therapy	• Clinical diagnosis • Skin biopsy	1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Lymphoma • **HSTCL** • **PTLD**	Dual Anti-TNF + thiopurine therapy	• Cross sectional imaging • Tissue Biopsy	1. Stop drug 2. Consider switching drug class
Other malignancies: Leukoencephalopathy	Dual Anti-TNF + thiopurine therapy	• Clinical diagnosis • Imaging • Tissue Biopsy	1. Stop the drug 2. Consider switching drug class 3. Relevant Specialist involvement

Anti – TNF : Anti-Tumour Necrosis Factor ; HSTCL: Hepatosplenic T-cell Lymphoma; PTLD: Post-transplant lymphoproliferative disorder

CONCLUSION

The use of biologics is now standard therapy for IBD used either as monotherapy or in combination with immunomodulators. A review of safety data of currently used biologics show cumulative evidence for anti-TNFα as they have been used for longer duration. In summary, acute infusion reactions are common with anti-TNF, neutropenia is a worrying AE and may require temporary cessation of therapy. Infections are significantly higher with anti-TNF which include common and uncommon bacterial infections, mycobacterial infections (in particular TB), viral and fungal infections and opportunistic pathogens. Diagnostic and management strategies are outlined in separate tables.

Anti-TNF therapy causes a wide range of dermatological presentations. It is important to differentiate drug induced psoriasis from psoriasiform rash. Treatment may range from topical therapy to anti-TNFα withdrawal. Ustekinumab may be useful in these cases.

Malignancies thought to be linked to anti-TNF use include solid organ malignancies, NMSC, melanoma, lymphoproliferative malignancies, and those with a viral association. However, difficulty remains in attributing a causal relationship particularly given the confounding of thiopurine use. The link between HSTCL is recognised but currently not quantified due to scarcity of data. IBD increases risk for NMSC, with the risk further increased for in combination therapy. The risk of lymphoma is increased with combination therapy with thiopurines including EBV related lymphoma but it is to be noted that results from the TREAT registry suggest that none of the immunosuppressants, infliximab or combination therapy are an independent risk factor for malignancy. However, the follow up duration remains short. Biologics can be used in patients with prior history of cancer after careful discussion about risks and benefits with oncologists.

Finally, although these therapies are often very effective, they present unique challenges. It is likely that in the future biologics will be used in a wider cohort of patients earlier in their disease journey, and therefore prompt recognition of adverse events secondary to drugs is important. Further reporting of rarer AEs and prompt recording of common AEs in registries will help assess risk more accurately. This information should help clinicians inform their patients of risks associated with each therapy and will lead to more informed decision making, thus improving patient care.

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Review article: Managing the Adverse Events Caused by Anti-TNF Therapy in Inflammatory Bowel Disease

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STRUCTURED SUMMARY

Background

Biological therapy is currently widely used to treat inflammatory bowel disease (IBD). Infliximab, adalimumab and golimumab are currently licensed anti-TNF therapies. Biosimilar anti-TNF monoclonal antibodies are increasingly used. Anti-TNF therapies are most widely used and their adverse effects are best characterised, which may cause significant morbidity and mortality in a small proportion of exposed patients. Gastroenterologists need to understand the mechanism for these effects, recognise these swiftly and manage such events appropriately.

Aim

This review aims to cover the range of potential adverse reactions as a result of biologic therapy and specifically management of these events.

Methods

A Medline and Pubmed search was undertaken. Search terms included were “anti-TNF”, “infliximab” or “adalimumab” or “golimumab” combined with the keywords “ulcerative colitis” or “Crohn’s disease” or “inflammatory bowel disease” and then narrowed to articles containing the keywords “complications”, “side effects” or “adverse events” or “safety profile”. International guidelines were also reviewed where relevant.

Results

Adverse events discussed in this review include infusion reactions, blood disorders and infections (including bacterial, viral, fungal and opportunistic infections) as well as autoimmune, dermatological disorders, cardiac and neurological conditions. Malignancies including solid organ, haematological, and those linked to viral disease are discussed.

Conclusions

Anti-TNF therapy has wide-ranging effects on the immune system resulting in a spectrum of potential adverse events in a small proportion of patients. Research advances are improving understanding, recognition and management of these adverse events.

INTRODUCTION

The use of biologics is currently approved for moderate-to-severe Crohn's disease (CD) and moderate to severe ulcerative colitis (UC)[1-9]. Infliximab, adalimumab and golimumab are antibodies to tumour necrosis factor-α (TNFα). These drugs work on a common pathway of blocking TNFα, a pro-inflammatory cytokine closely linked to acute phase reaction and systemic inflammation, thereby reducing the degree of damage to tissues. These have been developed using different techniques therefore conferring different degrees of immunogenicity. [Infliximab (human-chimeric), adalimumab (fully human), golimumab (fully human), certolizumab (recombinant pegylated humanised Fab' fragment)].

These medications have transformed medical treatment options for inflammatory bowel disease (IBD) in recent years and are prescribed in increasing numbers. As there are less golimumab exposed patients than the other two anti-TNF monoclonal antibodies, less adverse effects have been reported but generally most adverse effects are class effects. Clinicians need to be aware of & recognise adverse events (AE/AEs) that may result from the use of these drugs and also have clear management strategies in different scenarios. This comprehensive review summarises a range of possible AEs providing evidence based guidance where available and pragmatic guidance for areas where evidence is lacking.

AIMS AND METHODS:

A MEDLINE and PUBMED search was undertaken by (U.S, C.L) for articles pertaining to adverse effects of anti-TNF therapy in IBD. After an initial title screen, all relevant articles were examined in full. The main aim of the review is to focus on management of adverse events caused by anti-TNF therapy. For clarity, these AEs are discussed in categories as per systems, alongside recommended course of action including any further investigations or management. Where relevant, this manuscript also refers to international guidelines.

Non-infectious complications and management strategies

Hypersensitivity reactions

Hypersensitivity reactions vary widely in presentation, ranging from acute infusion reactions to delayed hypersensitivity.

- Type I acute hypersensitivity reactions (IgE mediated) present as anaphylaxis
- Type II are cytotoxic; complement-mediated
- Type III are immune-complex related presenting as serum sickness
- Type IV are cell-mediated delayed hypersensitivity; mediated by T lymphocytes

Acute infusion reactions (IR) are defined as those which occur during or within 24 hours of the infusion. The symptoms vary and reactions can range from mild (flushing, dizziness, headache, itching, rash) to severe (anaphylactic-like)[2]. Acute infusion reactions are relatively common, estimated to occur in up to 5% of infusions, with less than 1% of all infusions resulting in a severe reaction[3].

Patients with antibodies to infliximab are at an increased risk of infusion reactions[4] and case reports suggest hypersensitivity to adalimumab are also associated with adalimumab antibodies[5]. A review by the Food and Drug Administration (FDA) reported that injection site reactions were more common with adalimumab[6] with higher reporting odds ratio(ROR) in the 20-29y age group (ROR=16.18). The ROR was seen to reduce with increasing age[6]. Injection site reactions to golimumab in the PURSUIT

study were low at 3.4% with no reported anaphylaxis or delayed hypersensitivity to 6 weeks[7]. Delayed reactions (24 hours to 14 days) presenting with arthralgia, myalgia, fever, fatigue and rash are much rarer (<1%)[3]. The pathophysiology of immunologic features are not completely understood[8].

Management

The management of IRs is generally similar regardless of which agent has caused it. Typically, symptoms improve substantially or resolve completely after infusion rate adjustments and treatment with paracetamol, antihistamines or corticosteroids are provided. Evidence to support the use of premedication with corticosteroids or antihistamines is limited, with patients still experiencing infusion reactions despite pre-medication[9] and therefore should be considered on an individual basis. Injection site pain due to adalimumab can be reduced by using low volume formulations which are free from citrate buffers, with no change in efficacy[10].

In severe acute reactions, it is recommended that infusion is stopped and focus should be on maintaining airway, circulation as per standard anaphylaxis guidelines[11]. (Table 1) Delayed infusion reactions are typically managed by antihistamines, paracetamol and corticosteroids. A systematic review looked at management of infusion reactions and presented useful algorithms to manage mild, moderate and severe reactions[12]. These algorithms are simple, and a pragmatic tool to use for the vast majority of reactions seen in clinical practice[12]. After a hypersensitivity reaction, it is pragmatic to obtain therapeutic drug levels and anti-drug antibody levels.

Table 1- Hypersensitivity reactions to anti-TNF therapy

Complication	Diagnosis	Management Strategy
Type 1 Hypersensitivity This is more common when antibody titres are high. Incidence is higher during re-introduction of drug**s**	• Clinical diagnosis • Serum mast cell tryptase • Detection of antibodies on serum analysis where available	1. Mild reactions: Slow infusion rates 2. Consider hydrocortisone injections as a pre-administration medication 3. Anaphylaxis reactions: Treat as per ALS pathway with adrenaline, steroids and anti-histamines
Type 2 Complement Mediated Non-specific symptoms	• Detection of antibodies on serum analysis where available	1. Symptomatic treatment 2. Consider stopping treatment
Type 3 Immune-Complex Mediated Serum sickness	• Difficult to detect on assays, immune complexes known to adhere to membranes	1. Symptomatic treatment 2. Consider stopping the drug and switch if antibodies are confirmed
Type 4 T-Cell Mediated Delayed hypersensitivity reaction (after 24 hours up to 14 days post-infusion).	• Clinical diagnosis	1. Symptomatic management 2. Consider stopping drug

Anti – TNF: Anti-Tumour Necrosis Factor; ALS: Advanced Life Support

Haematological effects

Leucopoenia

Neutropenia has been reported in anti-TNFα treatment-exposed patients, with up to 20% of patients developing neutropenia on at least one occasion[13]. TNFα up-regulates other pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8, and granulocyte–macrophage colony-stimulating factor, involved in the differentiation and maturation of haematopoietic progenitor cells[14]. TNFα blockade could mediate bone marrow failure by inhibiting stem cell differentiation[15]. However, the reduction in neutrophil count following TNFα inhibitor therapy is not seen for other cells from the same lineage (myeloid progenitor cell), specifically basophils, eosinophils and monocytes. The risk of neutropenia is significantly higher in patients with a low baseline neutrophil count or a previous history of neutropenia[13,16].

Thrombocytopenia

Isolated thrombocytopenia following the use of anti-TNF drugs[17,18] has been reported. There are multiple hypotheses as to the possible aetiology, including autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes triggering the complement cascade, another unknown autoimmune mechanism, or idiosyncratic reaction[18].

Anaemia

Anaemia is considered a marker of active disease in IBD and therefore clinicians need to first consider this as an aetiology. The incidence and prevalence of anaemia was approximately 19% and 28% respectively, in a recent population based cohort study. Crohn's with stricturing disease and long-standing UC were recognised as risk factors[19]. One study showed only marginal improvement in anaemia after treatment with anti-TNF therapy suggesting that disease activity in itself has a major role to play[20].

In this section, anaemia directly attributable to biologics is discussed, which is rare. There are sporadic case reports of aplastic anaemia with infliximab, more commonly in patients with rheumatoid arthritis than IBD[21]. A single case of infliximab induced autoimmune haemolytic anaemia (in a patient found to be anti-nuclear antibody (ANA) positive 1:40) has also been reported[22].

Management of haematological effects

All patients starting anti-TNF therapy should have a baseline complete blood count with repeat testing every three to six months. At the onset of neutropenia, the anti-TNF should be withheld if the neutrophil count is deemed too low by the clinician. The patient should be left drug-free until neutrophil counts recover & anti-TNF therapy restarted when deemed clinically safe. Neutropenia can occur in patients managed with combination therapy with an anti-metabolite and this should be borne in mind and should be discontinued first. A neutrophil count less than 1000/mm^3 should raise concern and <500/mm^3 should lead to discontinuation of incriminating drugs and close monitoring. Rare anti-TNF induced systemic lupus erythematosus should be excluded and sargramostim is rarely necessary after drug discontinuation.

Thrombocytopenia can be managed by drug cessation, corticosteroid therapy or rescue therapy with intravenous immunoglobulin (IVIG). Thrombocytopenia has been reported to be prolonged after cessation of therapy. In severe cases this could persist for up to 6 months and also preclude exposure to any further anti-TNF agents[18]. This is likely to be a class effect and re-challenge with same class could be risky and therefore discouraged[17]. In severe cases, specialist haematology input is suggested.

Anaemia in IBD is more commonly seen due to ongoing disease activity. Clinicians should first consider assessment for disease and strategies to control and manage anaemia secondary to disease as per guidelines. As anaemia related only to therapy is rare, there is no specific guidance in current literature regarding future therapy with anti-TNF. Cessation of therapy would depend on

careful physician-patient discussion taking into account the severity of anaemia and alternative treatment strategies. Involving haematologist in refractory cases would be prudent. (Table 2)

Table 2- Haematological complications with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Leucopenia **Neutropenia**	• Blood count monitoring	1. If < safety threshold: stop drug, monitor blood count 2. Restart drug when counts are within normal range 3. Monitor 4. Consider G-CSF
Thrombocytopenia	• Blood count monitoring • Establish temporal relationship to drug • Secondary cases of low platelets to be excluded including concomitant drug therapy	1. If < safety threshold: stop drug, monitor platelet count 2. Consider IV immunoglobulins & steroids 3. Consider switching to different class of biologic
Anaemia Drug related anaemia is rare but aplastic anaemia can be serious	• Blood count monitoring • Bone marrow aspiration in refractory cases	1. If aplastic anemia: withdraw and stop drug 2. Refractory cases warrant specialist hematology assessment

G-CSF- Granulocyte-Colony Stimulating Factor

Dermatological effects

In addition to skin malignancies anti-TNF therapy can cause a wide range of dermatological conditions. Most notably they include local skin irritation or reaction, increased skin infection rates, psoriasis, eczema, acne, and alopecia. Other rare dermatological complications include erythema nodosum[23], granuloma annulare and interstitial granulomatous dermatitis. Although some of the above complications are also seen as extra-intestinal manifestations of disease, temporal association with biologic therapy should help differentiate disease related complications from drug related complications.

Psoriasis and psoriasiform reactions can occur directly as a result of anti-TNFα therapy, which interestingly is used by dermatologists to treat severe cases of psoriasis. Psoriasis is a relatively common side effect of anti-TNFα therapy, with 1.5-5% of patients developing this manifestation[24]. It is seen most commonly in females, typically 2-6 months following initiation of therapy[25]. A nation-wide cohort study reported incidence rates of anti-TNF induced psoriasis in IBD at 0.5% per patient-year[26]. A more recent study shows a much higher incidence at 10.5%[27], but psoriasiform lesions are more common than psoriasis and have distinctive features. According to current evidence, females, smokers and patients with fistulising disease appear to be at risk[27]. In addition to anti-TNFα induced psoriasis, psoriasiform and drug-induced psoriasiform lesions have been well recognised. Psoriasiform drug reactions can be distinguished histologically from psoriasis and resolve swiftly on cessation of drug therapy. Re-challenge results in recurrence of the lesions. The psoriasiform lesions could be secondary to infections and resolve on its treatment, though the infective origin of these are not always clear nor are their implications[25].

The exact mechanism triggering de novo psoriasis is unclear, although it has been postulated to be secondary to increased cutaneous expression of interferon alpha (IFNα). IFNα is released from dendritic cells to recruit T cells and pro-inflammatory cytokines IL-12 and IL-23. TNFα would

normally block IFNα expression and so anti-TNFα results in up regulation of IFNα[24]. Higher levels of IFN are seen in anti-TNFα induced psoriasis than idiopathic psoriasis[25].

Management

Management of psoriasis due to anti-TNFα depends on severity of symptoms. Milder cases of psoriasis can be treated clinically with topical therapy without cessation of anti-TNF, however more severe cases may require anti-TNFα withdrawal[24]. About 80% of patients respond to a combined approach of steroids and biologics withdrawal[26]. The use of another anti-TNFα agent may result in recurrence of psoriasis in majority of cases (52%)[25]. Ustekinumab has been used in the treatment of CD[28] and psoriasis[29]. There have been rare reports of paradoxical worsening of psoriasis with ustekinumab but not known to cause drug-induced psoriasis[21]. Ustekinumab is potentially an attractive option for treatment of refractory anti-TNFα induced psoriasis[25] requiring withdrawal of primary drug. Methotrexate has been used but does not appear to be effective in all cases[26]. It is a useful option to have in selected cases. (Table 3)

Table 3- Dermatological adverse effects with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Psoriasis Relatively Common (1.5% - 5% of patients on anti-TNFs)	• Clinical diagnosis • Histology of skin lesions • Establish temporal relationship between initiation of biologic therapy and development of psoriasis	1. Specialist involvement from dermatology 2. In mild cases: topical steroid therapy 3. In severe cases: stop drug and consider alternatives such as Methotrexate 4. Ustekinumab for managing both conditions is a viable alternative
Psoriasiform lesions Common	• Clinical Diagnosis • Consider skin infections causing the rash	1. Consider stopping drug in severe cases. 2. Responds well to cessation of drug therapy 3. Treat skin infection as appropriate
Erythema Nodosum **Granuloma Annulare** **Interstitial Granulomatous Dermatitis** Very rare	• Clinical Diagnosis	1. No clear evidence on management as these conditions are rare 2. Specialist dermatology involvement is advised 3. Usually not necessary to withhold or stop drug 4. Clinician decision based on risk: benefit assessment

Anti – TNF : Anti-Tumour Necrosis Factor ;

Autoimmune-like disorders

Autoimmune-like disorders/syndromes are a group of conditions observed in patients on anti-TNF therapy. This was first described in initial studies of infliximab in patients with rheumatoid arthritis[30]. These disorders include a variety of conditions such as positive antibodies e.g. –anti-nuclear antibodies, anti-double stranded DNA antibodies (dsDNA) (commonly IgM type), on immunological testing, various systemic or organ-specific autoimmune diseases as documented in the BIOGEAS registry, drug-induced systemic lupus erythematosus (DIL) called lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optical neuritis & inflammatory ocular disease, multiple sclerosis (MS)-like central nervous system (CNS) demyelination and peripheral neuropathies[31].

William et al described anti-TNFα induced lupus (ATIL) based on the severity of symptoms displayed and suggested that ATIL is a distinct syndrome in itself[32] and are likely to be different from drug induced lupus. In a pooled analysis across various diseases, studies which included patients with IBD showed that whilst ANA positivity was very common after anti-TNF therapy (40%-56%), asymptomatic anti-nuclear antibodies or anti-double stranded DNA antibodies require observation but not discontinuation of anti-TNF. The full range of symptoms of ATIL was seen in only about <1% of patients[32]. Most patients with full blown ATIL had fever, rash, arthritis and haematological abnormalities.

A large case series was reported by Costa et al comparing drug-induced lupus secondary to anti-TNF and classic drug-induced lupus[33]. Both groups had similar systemic features and symptoms but there were some features that distinguished one group from the other. 72% of patients with anti-TNF drug-induced lupus had cutaneous manifestations compared to about 25% in classic drug-induced lupus group. Classic drug-induced lupus was not usually associated with antibodies to dsDNA and extractable nuclear antigen (ENA) or with complement consumption. 90% of anti-TNFα

drug-induced lupus patients were positive for anti-dsDNA antibodies and >50% had anti-extractable nuclear antigen antibodies and decreased serum complement levels[33].

Management

The management of autoimmune-like disorders/syndromes secondary to anti-TNF therapy requires a customised therapeutic approach according to severity of the induced autoimmune disease. ATIL should be considered a distinct condition and managed accordingly. There are features which could help distinguish this. The incidence/prevalence of dsDNA antibodies and hypocomplementaemia is greater in ATIL, whilst anti-histone antibodies, the hallmark of classic drug-induced lupus, are less commonly found[32].

In patients with a positive ANA, it is not in itself an indication for discontinuation of therapy. In the presence of mild features, cessation of therapy is probably sufficient. However, it can be continued in patients with isolated cutaneous lesions or immunological alterations in whom biologics are thought to be essential to treat underlying disease, with closer follow-up. In patients with involvement of internal organs (kidney, lungs, nervous system), cessation of therapy is mandatory with addition of corticosteroids and/or immunosuppressive agents[30,33]. After discontinuation of the incriminating anti-TNF the prognosis is generally very favourable. The presence of diagnosed SLE is a contraindication to anti-TNF exposure.

Cardiac effects

It was reported that worsening cardiac failure was a possible adverse event in a randomised controlled trial investigating the use of anti-TNF therapy in cardiac failure[34]. Majority of patients enrolled were New York Heart Association III (NYHA) at baseline and the group receiving high dose infliximab (10 mg/kg) were adversely affected with an increased likelihood of hospitalization, high

frequency of worsening heart failure, with the risk of adverse clinical events persisting for up to five months after cessation of therapy[34]. The exact mechanism of heart failure with anti-TNFα use remains unclear.

There have been case reports of second degree and complete heart block after infliximab therapy but are rare[35]. This is more likely to happen in rheumatological conditions as there may be underlying cardiac involvement. A single blind prospective study which included rheumatological conditions concluded that new-onset cardiac arrhythmias, particularly ventricular tachyarrhythmia, developed during infliximab infusion, but their incidence did not achieve statistical significance[36]. Acute coronary syndrome following infusion has been reported but this too is very rare[37]. The rarer cardiac effects are based on reports with a very small number of patients, mostly from the rheumatology cohort who are at higher risk of having cardiac disorders.

Management

Current guidance recommends that use of anti-TNF therapy is best avoided in those with NYHA III/IV heart failure[38]. All patients who develop heart failure while on an anti-TNF agent should discontinue therapy, conventional medication for treatment of heart failure started and specialty advice sought. An alternate class of agent should be considered for the primary disease process. It is still unclear whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYHA class I/II) [38]. For patients commencing anti-TNF therapy who have specific cardiac risk factors such as hypertension, valve disorders or ischemic heart disease, our recommendation is that clinicians should get a baseline electrocardiogram to record QT interval among other features and clinically assess the patient for any features of pre-existing heart failure that may preclude therapy. Not all studies have substantiated an association of anti-TNF therapy with heart failure and this is rare in patients with IBD.

Table 4- Cardiac adverse effects with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Cardiac Failure	• Clinical diagnosis • Objective assessments with investigations	1. Avoid anti-TNFs in NYHA III and IV heart failure 2. If drug precipitates heart failure: stop the drug 3. Treat for heart failure with diuretics and early specialist involvement 4. Switch to another class of drugs
Second and third-degree Heart Block More commonly seen in the treatment of rheumatological conditions; less so with IBD	• 12 Lead ECG • Cardiac monitoring	1. Monitor patients for features of decompensation 2. Specialist involvement for further management 3. Stop drug and switch to another class
Arrhythmias More commonly seen in the treatment of rheumatological conditions; less so with IBD	• 12 Lead ECG • Cardiac monitoring	1. Usually transient and does not need any specific management 2. If transient episodes are self-limiting: consider continuing drug 3. If persistent: seek specialist cardiology opinion

Anti – TNF : Anti-Tumour Necrosis Factor; NYHA- New York Heart Association

Neurological effects

Demyelination

Demyelination has been recognised as a complication of anti-TNF therapy. A review of FDA adverse event recording system showed that among 772 reports of neurological complications, 18% of patients had IBD. About 36% of patients had received infliximab and peripheral neuropathy was the most commonly reported event[39]. Demyelination can occur in central or peripheral nervous systems[40]. It is unclear as to whether the relationship is truly causal, or whether anti-TNF triggers an existing tendency for demyelination.

Management

The patients who have a family history of demyelination disorders may be at higher risk and this should be considered before the therapeutic agent is chosen[41]. It is standard guidance to avoid anti-TNF therapy in patients with concomitant multiple sclerosis or history of optic neuritis. In patients who develop neurological deterioration and suspected demyelination during therapy, treatment with biologic agent should be discontinued[41] and specialist neurology opinion should be sought. The clear relationship between demyelinating events and anti-TNF can be difficult to establish as IBD may also be associated with demyelination. Treatment with corticosteroids, IVIG and plasmapheresis are rarely necessary. (Table 5)

Table 5- Neurological reactions with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Demyelination Known to worsen demyelination in patients with multiple sclerosis	• Clinical diagnosis • Nerve Conduction Studies • MRI	1. Stop drug and consider alternatives 2. Seek specialist Neurology involvement 3. Consider pulse therapy with high dose methylprednisolone 4. Consider IV Immunoglobulin

MRI-Magnetic resonance imaging

Infections and management strategies

Biologics are strong immunosuppressive agents and can increase risk of infection depending on their mechanism of action. TNFα is essential for activation, differentiation and recruitment of several immunological cell types; it has a role in granuloma formation, maintenance of granuloma integrity[42] and host response to mycobacteria and intracellular organisms[43]. A recent meta-analysis found that anti-TNF therapy was associated with a greater infection risk than placebo in treating UC but anti-integrin therapy was not; neither class showed an increased infection risk over placebo in CD[44]. Other studies have confirmed increased risk in both forms of IBD.

A recent systematic review by Wheat et al concluded that at present there is no evidence of a higher odds of serious infection from the newly available biologic therapies such as vedolizumab and ustekinumab compared to anti-TNFs[45]. Feagan et al report that infections in patients exposed to ustekinumab for CD is no higher than placebo in UNITI trials[46] and Wils et al reported 1 serious pulmonary infection in a cohort of 122 ustekinumab patients, followed up over 2 years[47]. Bye et al reported an increased risk of Clostridium difficile infection with vedolizumab therapy but concomitant steroid and narcotic analgesics were identified as risk factors[48].

Bacterial infections

Patients receiving anti-TNF therapy have been reported to acquire both common and uncommon bacterial infections. Common sites for infection include upper and lower respiratory tracts, skin and subcutaneous tissue, urinary tract and GI tract[49].

Management

Common infections are treated with oral antibiotics as per local guidelines. A pragmatic approach would be to have a lower threshold to start treatment and switch to intravenous drugs in the presence of systemic symptoms. In severe sepsis requiring prolonged antimicrobial treatment, anti-TNF

therapy may have to be withheld. Restarting therapy can be considered once patients are afebrile, white cell counts within normal range and relevant imaging (CT, MRI pelvis) show no evidence of infective source. (Table 6)

Uncommon infections

Several non-mycobacterial intracellular infections, including listeriosis caused by *Listeria monocytogenes* and legionnaires' disease most often caused by *Legionella pneumophilia* , have been associated with anti-TNF therapy[50]. Listeria sepsis and meningitis has been described in patients receiving anti-TNF drugs[51] and in 2011, the FDA added a boxed warning about the risk of listeriosis and legionnaires' disease for the entire class of TNFα inhibitors[52]. There are a few case reports of listeriosis complicating anti-TNF therapy. Listeriosis carries significant mortality, therefore requiring prompt diagnosis and aggressive treatment. The risk appears to be higher during the first year of therapy[53]. Anti-TNF should be discontinued till the patient recovers from listeriosis.

Management

Suspicion of infection requires confirmatory testing and treatment using standard antibiotic regimes depending on pathogen isolated. Listeriosis is more likely to be seen in patients consuming mould-ripened cheese regardless of whether it is from pasteurised or unpasteurised milk and also from cold smoked gravad fish[54]. In one study from USA, unpasteurised milk and dairy products were noted to significantly increase the risk of infections caused by *E-coli, Salmonella and Campylobacter*[55]. In view of this overall increased risk of infections, it is safer for patients to avoid consumption of unpasteurised milk whilst on anti-TNF drugs.

Mycobacteria and tuberculosis

Tuberculosis (TB) caused by mycobacterium bacilli is a serious infection which carries significant morbidity. TNFα is necessary for a Th1-based cell-mediated immune response important in

activating macrophages to kill intracellular mycobacteria, and limit spread by formation of granulomas[56,57]. The majority of exposed immunocompetent hosts have latent TB (LTB) which can subsequently lead to reactivation of infection if there is compromise to the immune system, such as initiation of anti-TNF drugs[58]. It is therefore critical to identify and treat LTB prior to starting anti-TNF therapy[58].

An association between anti-TNF therapy and development of TB was noted when the FDA MedWatch spontaneous reporting system demonstrated 70 TB cases in a median of 12 weeks after initial infliximab exposure, in 2001[59-68]. Both extra-pulmonary and disseminated TB are more common in patients treated with anti-TNF therapy, compared with immunocompetent patients[59-60]. It has been hypothesised that the early occurrence of TB after infliximab may suggest reactivation of LTB rather than a de novo infection[60]. Due to the high risk of reactivation, screening for TB is recommended prior to starting anti-TNFα.

The diagnosis of LTB can be difficult and should include a combination of detailed history and supportive investigations. At present, IGRA (interferon gamma release assay) and TST (tuberculin skin test) are commonly used in most centres. In a study by Mariette et al which looked at how effective the available tests are, it was noted that when one of the IGRA tests replaced TST, it influenced the decision made by physicians, leading to 28% fewer patients receiving anti-TB (ATB) prophylaxis[61]. This is likely because IGRA tests are more specific. As per this study, IGRA does not appear to be affected by corticosteroid or immunosuppressant therapy[61]. However, this may not always be the case as shown in an *ex vivo* study in which corticosteroids and infliximab reduced the performance of IGRA[62]. At present, IGRA is possibly more reliable than the other options available. TST is less specific and can be less frequently positive due to corticosteroid or immunosuppressant therapy and this should be borne in mind. Based on their findings, Mariette et al proposed the an algorithm for assessing patient, which is now generally applied prior to starting anti-TNFα therapy[61]. All patients should undergo appropriate history +/- chest x-ray. For those with a positive history or

x-ray, treat with ATB prophylaxis. For those with negative history, check with IGRA test (authors recommend GOLD, followed by T-SPOT if indeterminate). Those with negative results require no further screening. Those with positive results require ATB prophylaxis. Patients with indeterminate GOLD and T-SPOT test should undergo TST testing. Negative results require no further action, but a positive TST should be treated with prophylaxis[61].

In patients who have a positive TST and negative IGRA, the degree of clinical suspicion should guide management, based on history and chest x-ray with a very low threshold to treat the patient. Generally, performing both TST and IGRA is not recommended. An initial indeterminate borderline IGRA can be followed up with TST and if the latter is positive the patient should be treated. The CDC recommend testing with either IGRA or TST, but a combination of both may be appropriate where clinical suspicion of LTB is high, or risk of subsequent LTB reactivation may result in a poorer outcome (such as those on immunosuppressants)[63].

Management

Guidelines by European Crohn's and Colitis organisation (ECCO)[26] and British Thoracic Society (BTS)[58] on screening and management of TB are similar in principle, suggesting treatment of LTB prior to initiation of anti-TNF therapy with a complete therapeutic regimen. If there is clinical suspicion +/- radiographic changes suggestive of TB, patients should be referred for treatment of LTB[58]. Other patients should undergo LTB screening tests. The optimal screening strategy for these patients is still debatable.

After diagnosis of latent TB in a patient with IBD, appropriate treatment should be administered for at least 3 weeks prior to commencement of anti-TNF therapy[64,65] ; however if treatment with anti-TNF therapy is considered very urgent simultaneous treatment for latent TB and IBD may be considered. Alternative therapies such as vedolizumab or ustekinumab may also be considered for UC or CD. Short latent TB therapies are increasingly considered such as rifampicin for 4 months or isoniazid plus rifampicin for 3 months as adherence to 9 months of daily isoniazid poses

challenges[66,67]. Exposure to active TB during anti-TNF therapy should lead to prompt re-evaluation for latent or active TB. In case of active TB, anti-TNF should be discontinued and active TB treated. If absolutely necessary, anti-TNF may be resumed after at least 2 months of anti-TB therapy with satisfactory response, though it may sometimes be resumed earlier if absolutely necessary. Increasingly other monoclonal antibodies such as ustekinumab or vedolizumab are being considered. Annual re-testing for LTB in patients on anti-TNF therapy depends on risk factors for exposure to TB and desirable in geographical areas with endemic TB. (Table 6)

Table 6- Bacterial infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Common bacterial infections		
Respiratory Tract **Urinary Tract** **Gastrointestinal** **Cellulitis**	• Clinical diagnosis • Relevant investigations depending on symptoms	1. Appropriate antibiotics based on site of infection 2. Consider early therapy 3. If any signs of sepsis: stop drug 4. Restart biologics when good evidence of resolved infection. (WCC, imaging)
Serious Bacterial Infections:		
Listeriosis **Legionnaires' disease** **Septic Arthritis** **Septicemia**	• Serology • CT/MRI of brain • Lumbar puncture if meningitis suspected	1. Appropriate antibiotics based on sensitivity 2. Seek specialist microbiology advice
Tuberculosis (TB):		
Latent TB Re-Activation	• Risk assessment based on initial screening with Quantiferon or T-Spot Testing • Thorough history and risk factor assessment • Chest X-Ray	1. If positive or indeterminate: involve specialists 2. Treat as per ECCO guidelines and British Thoracic Society Guidelines 3. Risk: Benefit analysis by clinician 4. Consider alternative therapy i.e. vedolizumab or ustekinumab

WCC-white cell count

Viral infections

A majority of human viral infections are self-limiting but some are capable of causing chronic infection [e.g. human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)]. There are viruses linked to malignancy, such as Epstein-Barr virus (EBV) and human papilloma virus (HPV). EBV will be discussed in more detail in 'malignancy' section of this text.

Varicella (VZV) and Shingles

This can present with severe or disseminated disease if contracted while on anti-TNF therapy[68]. In one study, the prevalence of prior varicella zoster virus (VZV) infection among IBD patients was greater than 90%[69] and it was not noted that a significant number had a VZV IgG negative status. It is known that patients with IBD are at a higher risk of VZV infection and more so when on immunosuppressive therapy[7071].

Herpes zoster or shingles is caused by reactivation of VZV. The incidence of shingles is again increased in patients with IBD, the elderly population at particular risk. In a study looking at herpes zoster in IBD, it was seen that patients with CD were at higher risk; age >45 years, treatment with corticosteroids for >2 weeks, thiopurine therapy were associated with increased risk of infection[72]. Long et al reported similar findings and also noted that patients on anti-TNF therapy for IBD are at higher risk of herpes zoster with an odds ratio of 1.81 (95% CI: 1.48-2.21)[73].

Management

Immunocompromised patients exposed to VZV should be treated with VZV immunoglobulin[74]. Patients who contract VZV or shingles during a period of immunosuppression require antiviral therapy. If oral therapy is appropriate, valganciclovir should be considered as this provides higher oral bioavailability than aciclovir[75]. (Table 7)

Prevention of infection is possible due to availability of effective vaccines. It is recommended that all patients are screened for evidence of past infection prior to starting biologics or immunosuppressives including steroids. ECCO suggest that in seronegative patients two-dose course of varicella vaccine should be given at least 3 weeks prior to commencement of therapy[65]. If subsequent immunisation is necessary, it can be administered after a 3–6 month cessation of all immunosuppressives as both the VZV and shingles vaccines are live vaccines[75], although there is emerging evidence that administration of live zoster vaccine to patients already on anti-TNF therapy did not result in disease and there was expected immune response to the vaccine[73].

Hepatitis B

TNFα and interferon (IFN)γ are released by cytotoxic T lymphocytes on antigen recognition of the hepatitis B virus (HBV), activating two viricidal pathways, plus antigen non-specific T cells & macrophages[76]. Reactivation of HBV may occur during anti-TNF therapy, or on subsequent withdrawal (secondary to immune reconstitution). Reactivation of chronic HBV carriers (hepatitis B surface antigen (HBsAg) positive, undetectable HBV DNA, normal LFTs) after anti-TNF therapy has been reported[77]. Patients who have had HBsAg seroconversion following exposure to HBV [HBsAg negative, anti-HBc (core antibody) positive and anti-HBsAg antibody positive] have been successfully treated with anti-TNF therapy without HBV reactivation during follow up[78]. Chronic active HBV patients already successfully controlled with antiviral therapy prior to introduction of anti-TNF show no deterioration in the viral load or liver enzymes[79,80]. A comprehensive review by Pattullo[81] looked at incidence & prevalence of HBV reactivation in IBD when treated with immunosuppressants without HBV prophylaxis; risk stratification of patients was also done based on type of biologic therapy[81]. The incidence of immunosuppression related HBV reactivation was noted to be about 36% in HBsAg positive patients. The overall prevalence of HBV in IBD ranged from 0.6-17% for HBsAg positive patients, and 1.6-42% for HBsAg negative/anti-HBc positive

patients. The risk estimate of HBV reactivation was reported to be moderate (1-10%) with anti-TNF[81].

Management

All patients should be screened prior to initiation of therapy, although which patients should receive antiviral therapy remains unclear. Screening should be carried out checking for hepatitis B surface antigen, antibody to surface antigen & anti HB core antibody levels and if HBsAg or anti-HBc is positive, DNA quantification should be done[65]. Chronic HBV carriers and those with HbsAg seroconversion should be considered for antiviral therapy and hepatology involvement. It is recommended that patients who are due to start biologics (moderate risk) are given anti-viral prophylaxis if they are HBsAg positive and continued for at least 6 months after completion of immunosuppressive therapy[81]. In case of reactivation, it is recommended that one of the antivirals is started and continued for at least 6 to 12 months after immunosuppressive therapy has been stopped. The antiviral medication of choice may depend on the patient's individual circumstances, and the planned duration of immunosupression[82]. Entecavir and tenofovir are now preferred anti-virals in IBD patients due to their rapid onset of action, highest anti-viral potency with low incidence of resistance[65]. Whilst lamivudine is used, this has its limitations if long term therapy is required, as resistance can occur in up to 30% of patients after 1 year and 70% after 5 years[82]. Peginterferon-alpha-2a (IFNα) is best avoided due to the risk of myelosuppression and also risk of exacerbating CD[65].

Hepatitis C

TNFα appears to be involved in the pathogenesis of HCV, with patients with higher serum TNFα levels less likely to respond to anti-viral therapy[83]. TNFα blockade may increase reactivity of peripheral T cells to antigen stimulation[83]. Biologics have an acceptable safety profile for use in patients with HCV and is not contraindicated in concomitant HCV infection. However, in the

presence of acute HCV, anti-TNF therapy is contraindicated[84]. In the presence of chronic HCV, the decision to treat with anti-TNF depends on liver synthetic function. It is best avoided in patients who are Child-Pugh category B or C[84]. HCV patients being treated with anti-TNF therapy should have close monitoring of aminotransferases with consideration for discontinuation of treatment with continued elevations[83]. The guidelines from ECCO suggest cautious use of antivirals due to drug interactions[65]. Infection diagnosed whilst on anti-TNF therapy does not necessarily require cessation of therapy[65]. There is no data yet on the use of newer antivirals for HCV in the context of biologics use for IBD but there are no contraindications for their concurrent use.

Management

The ECCO guidelines are equivocal about screening for HCV prior to use of immunosuppressive therapy[65]. However, it would be prudent to screen patients who are likely to need biologics considering the high curative rates with newer anti-viral drugs for HCV. All patients with HCV infection should be discussed and managed jointly with hepatology services, especially when biologics are indicated for IBD. During the course of therapy, close monitoring of liver functions is key.

HIV infection

The interaction between TNFα and the human immunodeficiency virus (HIV) has been the subject of much scrutiny. The molecular pathway by which HIV expression is upregulated by TNFα is well described[85,86]. Despite these findings, use of anti-TNF in HIV-patients must be balanced with a potential increase in the risk of opportunistic infections in patients with an attenuated immune system.

The evidence base for advice regarding use of biologics in patients with HIV and IBD is limited. Within a cohort study and several case reports, biologic therapy with infliximab in refractory IBD patients has been demonstrated to be effective in inducing disease remission with only a minority

experiencing adverse effects[87-77]. It is important to note that initial CD4+ count in patients included in these studies are > 200 cells/mL. The ECCO guidelines[65] also suggest that the HIV-IBD cohort of patients are less predisposed to infection on highly active anti-retroviral therapy (HAART) than if they did not receive HAART. In this cohort, adverse effects have presented as either a pre-disposition to infections, deranged CD4+ count or HIV viral loads.

Abreu et al describe an HIV positive, thiopurine-intolerant patient treated with IFX for a UC-flare unresponsive to steroids[88] who had been on ART (emtricitabine/tenofovir/efavirenz) with undetectable HIV viral load & CD4+ count of 357/mmc prior to infliximab therapy. Although excellent disease response was achieved, he was diagnosed with listeriosis and was successfully treated. (CD4+ count 350/mmc). Infliximab was restarted with no clinical consequences. It is likely these patients with IBD remain at increased risk of opportunistic infections[89].

Other examples of adverse effects of biologics in HIV are reported in the rheumatology cohort[90]. In one case series[91], a patient who was not on HAART therapy was observed to have an increase in viral load (22,148 c/ml to 428,503 c/ml) following initiation of infliximab therapy. This required temporary cessation of infliximab and the rise was not observed at re-administration.

Within the limited evidence available, it is noted that patients do benefit from adequate disease response with no specific HIV-related complications. Due to risk of AEs, it is recommended that screening for HIV is undertaken prior to treatment with biologics and patients with IBD recognised as HIV positive are managed by a multi-specialty team. Generally, in the absence of other infections treatment of HIV infected patients with anti-TNF is relatively safe. This group of patients must ideally be on HAART. A discussion about potential increased risk of infection, baseline blood tests including CD4+ count (ideally 200 cells/mL+), and HIV viral load is necessary. Close monitoring throughout duration of therapy is key. An Increase in HIV viral load needs discussion with specialists and discontinuation of biologic may become necessary. Any overt sign of infection merits hospital

admission to identify and treat the infection source and biologics paused. Restarting biologics should be discussed based on clinical aspects of each case. (Table 7)

Table 7- Viral infections in the use of anti-TNF therapy

Complication	Diagnosis	Management Strategy
Varicella Relatively common	• Clinical diagnosis • Serology testing available	1. Treat with varicella immunoglobulin 2. Antimicrobial therapy with valganciclovir
Chronic Stable HBV Reactivation of chronic infection	• Screening for HBV mandatory • Close monitoring of liver function and viral load	1. Joint care with Hepatologist 2. May require treatment with antivirals 3. Biologics can be continued unless acute fulminant liver failure suspected
Chronic Active HBV on antiviral therapy	• Screening for HBV mandatory • Close monitoring of liver function and viral load	1. Continue antivirals 2. Entecavir and tenofovir drugs of choice
Hepatitis C	• Screening for HCV recommended prior to anti-TNF therapy • Close monitoring of LFTs and HCV RNA load in HCV infected patients	1. Joint care with Hepatologist 2. Continue biologic with close monitoring 3. No contraindication for therapy
Cytomegalovirus (CMV)	• Check serology for CMV IgM and viral PCR • Supported by tissue diagnosis with histology and immunohistochemistry	1. Treatment with IV ganciclovir and switch to oral valganciclovir for total of 2-3 weeks 2. Use foscarnet as per sensitivities 3. If systemic CMV infection: consider stopping anti-TNF
Human Immunodeficiency Virus	• Close monitoring in addition to CD4+ counts	1. Continue biologics when HAART established and CD4+ counts are above 350 2. Consider withholding biologic when CD4+ <200 3. Joint care with multidisciplinary decision approach

Anti – TNF : Anti-Tumour Necrosis Factor ; HBV-Hepatitis B virus; HCV-Hepatitis C virus; LFTs- liver function tests; PCR- polymerase chain reaction; HAART- highly active antiretroviral therapy

Fungal infections

Patients with IBD are known to be at an increased risk of fungal infections. This is due to multiple factors such as severity of disease activity, comorbidities, treatment with opioids, surgery, poor nutritional status, leucopenia and older age[92]. Another factor is immunosuppressive therapy, important of which are anti-TNFs. A risk factor analysis by one recent systematic review reported anti-TNF therapy as the predominant factor associated with fungal infections[92].

Aspergillosis

Aspergillosis, caused by *Aspergillus fumigatus* is a serious pulmonary infection which warrants prompt diagnosis and treatment. Attenuation of the inflammatory pathway through TNFα blockade alters the cytotoxic immune response to fungal infections and in aspergillosis, it is involved in polymorphonuclear leucocyte activation in response to infection[93]. The evidence is mostly from case reports. In 2001, a case of invasive pulmonary aspergillosis was reported in a patient with CD on anti-TNF therapy[94]. There have been other case reports since but overall, it appears to be a rare occurrence. This usually presents initially with a poorly productive cough and can progress to respiratory insufficiency; radiological changes are seen[94-95].

Management

The definitive diagnosis is on culture of broncho-alveolar fluid. The infection is treated with prolonged anti-fungal therapy based on sensitivities; amphotericin B or voriconazole or caspofungin is used. The condition carries very poor prognosis. Concomitant tuberculous cavity needs exclusion. (Table 8)

Histoplasmosis

This is another potential opportunistic infection reported in patients exposed to anti-TNF treatment. In a case series of ten immunocompromised subjects from an area endemic with histoplasmosis, 9

contracted histoplasmosis shortly after commencing infliximab infusions. Clinical presentation can be varied and include pulmonary, extra-pulmonary or disseminated disease symptoms which are non-specific[96].

Table 8- Fungal infections with anti-TNF therapy

Complication	Diagnosis	Management Strategy
Candidiasis Commonly localised infections but systemic and invasive infection can be life threatening	• Serology, culture and molecular studies	1. Localised infections: Topical therapy 2. Invasive infections: i. Stop biologic ii. IV Fluconazole iii. Seek specialist advice
Aspergillosis Pulmonary symptoms and invasive infection	• Serology, culture and imaging	1. Stop biologics 2. IV Anti-fungal therapy (Consider IV voriconazole) 3. Caspofungin is another option 4. Specialist involvement
Histoplasmosis Usually pulmonary infection	• Serology, culture and radiology	1. Stop biologic therapy 2. Treatment with either one of: i. Amphotericin B initially and step-down therapy to an azole preparation ii. Itraconazole
Pneumocystis Jirovecci	• Clinical diagnosis • Culture, microscopic and molecular diagnosis	1. Co-trimoxazole 960mg BD, if severe infection increases to 1.44 g BD 2. Specialist involvement

Management

Invasive fungal infections should be treated with systemic antifungals and all immunosuppressant medication should be reviewed. The FDA in 2008 have issued post market drug safety information alerting healthcare providers that invasive fungal infections and histoplasmosis in patients receiving anti-TNF drugs are not being swiftly recognised, resulting in possible delays to patient therapy. The FDA recommends the involvement of infectious diseases specialists[97] in the management of such cases. (Table 8)

Other Opportunistic infections

Cytomegalovirus (CMV)

CMV infection (detected by serology) could be due to reactivation of latent infection during immunomodulator or biologic therapy, but usually is itself mild or asymptomatic even on immunosuppressants. However, CMV colitis, retinitis, pneumonia or severe CMV infection during treatment of IBD requires further assessment[75] to plan management. Nevertheless, not all cases of CMV infection in anti-TNF use progress to CMV disease[98].

The diagnosis of CMV disease using histopathology with immunohistochemistry is highly sensitive and specific. This combined with CMV viral load (CMV DNA detected by PCR in serum & tissues) can provide most information about disease state[75]. CMV viral loads of >250 copies/mg is a predictor for patients presenting with corticosteroid-resistant disease[75].

CMV disease manifesting as colitis is a recognised complication of IBD and should be screened for in those patients presenting with acute severe colitis[99]. Typically, patients may have had previous exposure to immunosuppressive therapy and experienced prolonged corticosteroid therapy or corticosteroid-refractory disease. CMV can also be a cause of chronic pouchitis[100].

Management

It is important that diagnosis is established swiftly. When considered as a differential diagnosis, testing for CMV viral load with PCR is recommended to look for CMV disease especially in ill patients with systemic manifestations. Histology and immunohistochemistry may be used to support the diagnosis of CMV colitis. Once diagnosed, ECCO recommend a 2-3 week course of ganciclovir therapy for CMV disease, and immunosuppressants are withheld[75]. However, a retrospective cohort case study of CMV-positive colitides, identified that patients with milder colitis were less likely to be treated, and could respond to standard immunosuppressive therapy without additional treatment for

CMV. CMV may be transiently reactivated and disappear without antiviral therapy. In one study it was noted that those with more severe disease were more likely to be treated with ganciclovir, and were more likely to require either rescue therapy or surgery, despite adequate treatment of CMV[101]. CMV colitis complicating UC leading to acute severe colitis can be challenging to manage. A study by Kopylov et al reported that the outcomes for patients with severe colitis. Patients received infliximab/ciclosporin with ganciclovir vs ganciclovir alone, and they had similar colectomy rates[102]. In patients who test positive for CMV whilst on anti-TNF therapy, there is a evidence that anti-TNF can be continued[103]. (Table 7)

Pneumocystis pneumonia (PCP) or pneumocystis jirovecci pneumonia (PJP)

This is a serious infection reported in patients after use of immunosuppressants. A large population based cohort study looked at risk of PJP in IBD patients[104]. Although there is some evidence that the overall hazard risk of PJP in IBD is higher than normal population, the absolute risk of PJP is considered to be very low (0.03% in their cohort)[104]. In a large case series of PJP after infliximab use, mean onset of symptoms reported was 21 days although majority of patients were exposed to concomitant immunosuppressive therapy. Over a quarter (27%) of patients died[105] in these reported series, so early recognition and therapy is paramount. ECCO guidance recommends that patients on triple immunotherapy with one being a calcineurin inhibitor or anti-TNF should receive standard prophylaxis with Trimethoprim-sulfamethoxazole (co-trimoxazole) if tolerated. It should be considered in those on dual immunosuppression especially if one is a calcineurin inhibitor[75] and in anti-TNF regimens with associated corticosteroid use[75]. However, pill-burden and side effects are to be kept in mind. Co-trimoxazole is an effective option for prophylaxis and active infection. Clinicians should discuss with their local microbiology and infectious disease departments. Although more recent studies report very low risk, clinicians have to be vigilant throughout the course of treatment and decision on prophylaxis has to be on a case-by-case basis. (Table 8)

Infection prevention and vaccination recommendations

The main focus of the article is on management of adverse effects and our stress on prevention though very important, is limited as these have been extensively addressed in ECCO guidelines. ECCO guidance recommends that prior to immunosuppression a detailed history and examination including prior bacterial, viral and fungal infections, particularly herpes, VZV, TB exposure, prolonged travel/stay or plans to travel to TB endemic or tropical areas and completion of childhood vaccination programmes. Further advice should include cervical smear screening for women, food hygiene and avoidance of raw and unpasteurised foods. Education on safe use and preparation of dairy & meat products can benefit patients at risk of Listeria infection whilst on anti-TNFα therapy. Live attenuated vaccines must be avoided on immunomodulator or anti-TNF therapy and ideally patients should receive annual inactivated influenza vaccine and pneumococcal vaccine as required. Prior to the onset of immunosuppression, consider vaccination with any outstanding routine vaccines plus HBV, VZV (if seronegative and no clinical history) and HPV[75]. If patients require live vaccines during therapy, the risk: benefit assessment of vaccination should be undertaken. Patients are usually immunocompetent within 3-12 months[106] after cessation of therapy. Corticosteroid therapy alone is not considered to cause significant immunocompromise unless high doses (20mg or higher) have been used continuously for more than two weeks[106].

Malignancy

Malignancies thought to be linked to immunosuppressive agents and anti-TNF use include solid organ malignancies, non-melanoma skin cancer (NMSC), melanoma, lymphoproliferative malignancies, and those with viral association such as EBV-related lymphomas and HPV-related cervical cancers or dysplasia. However, difficulty remains in establishing a cause-effect relationship.

A possible association between anti-TNF use and malignancy first arose from post-marketing reports to the FDA. There were 26 cases of lymphoma reported in patients with rheumatoid arthritis or CD disease treated with etanercept or infliximab[107]. Further studies demonstrated an increased risk for solid organ and NMSC in patients treated with anti-TNF and further immunosuppressive therapies[108]. Many IBD patients are either on multidrug regimes or have had past exposure to thiopurines (or other immunosuppressants) prior to anti-TNF usage.

Historically most trial data is from the rheumatology population. A meta-analysis derived from nine clinical trials of patients receiving anti-TNF treatment or placebo identified a number needed to harm of 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months[109]. The malignancy rates were significantly more common in those treated with higher doses (≥6mg/kg of infliximab every 8 weeks or 40mg of adalimumab alternate weeks)[109]. A more recent meta-analysis of 74 randomised controlled trials concerning adalimumab and infliximab showed no overall relative risk (RR) increase on short term follow up for malignancy with the exception of NMSC which had a RR of 2.02 (95% CI 1.11-3.95)[110]. A 6-year follow up study from the national Danish registers only identified three solid organ malignancies and one case of melanoma, with total follow up ranging from 0.1-72.1 months[111]. The Crohn's therapy, resource, evaluation and assessment tool (TREAT) registry is collecting prospective data on large number of CD patients to evaluate the long-term safety of CD therapies. Data published from the registry in 2006 showed mortality rates to be similar

between infliximab and non-infliximab patient groups after a short period of follow up (mean follow up 1.9 years)[112]. Subsequent data from the registry published in 2014 (with follow up of up to 7.6 years) has shown that none of immunosuppressants, infliximab or combination therapy to be an independent risk factor for malignancy[113]. However, the follow-up period remains short and future analysis of the registry is likely to provide further evidence.

The CESAME Study Group[114] assessed the impact of thiopurine use on development of NMSC–comprised of basal cell carcinoma, squamous cell carcinoma and lymphoproliferative disorders (increased risk found in the thiopurine group). Although a large number of patients were included, the risk of malignancy secondary to biologics could not be assessed due to relatively small number of patients on these drugs[115]. A study by Long et al published in 2010 assessed risk of malignancy and concluded that IBD in itself increased risk of NMSC (incidence rate ratio IRR 1.64 95% CI 1.51-1.78) and a nested case-control model showed an increased risk because of recent biologic use among patients with CD (adjusted OR 2.07, 95% CI 1.28–3.33)[116]; patients on combination therapy had the highest OR compared to medication-free patients (OR 5.85 95%CI 3.2-10.8)[116]. Another study in 2012 reported that patients were at higher risk of melanoma when exposed to biologics and NMSCs were mainly related to thiopurine therapy[117]. The most recent French national cohort study showed an increased risk of lymphoma in treatment exposed patients. When compared with unexposed patients, the risk of lymphoma was higher among those exposed to thiopurine monotherapy (aHR, 2.60; 95% CI, 1.96-3.44; P <0.001), anti-TNF monotherapy (aHR, 2.41; 95% CI, 1.60-3.64; P < 0.001), or combination therapy (aHR, 6.11; 95% CI, 3.46-10.8; P < 0.001)[118].

There remains concern about cases of hepatosplenic T-cell lymphoma (HSTCL) (a rare and aggressive form of non-Hodgkin's lymphoma affecting predominantly young men) occurring following infliximab, adalimumab or thiopurine use. In a study published by Thai et al, they reported 22 cases of HSTCL in IBD and most were associated with thiopurine therapy either as monotherapy or in combination with anti-TNF. Whilst a link is recognised, quantifying this risk to individual patients

on current evidence is difficult[119].They also concluded that despite the risk, benefits of treatment far outweighed the risks[120].

Secondly, observational studies have noted a potential predisposition to development of EBV related lymphoproliferative disorders in IBD patients, in particular those treated with thiopurines and anti-TNFα agents[75]. Patients with EBV are predisposed to post-transplant lymphoproliferative disorders (PTLD), where T-cell immune surveillance is impaired[75]. EBV related lymphomas may present in the gut, rather than nodal sites. Screening for EBV should ideally be considered, however there is no current vaccination for EBV naïve patients. In those developing EBV on therapy, treatment with antiviral medication and withdrawal of therapy should be considered[75]. IBD itself does not appear to increase risk of lymphoma diagnosis[121]. However use of a thiopurine for IBD or combination therapy with an anti-TNFα may increase risk[121]. Establishing any isolated effect of anti-TNFα on lymphoma development is challenging. In a meta-analysis looking at lymphoma rates in CD patients treated with anti-TNFα, two thirds of all patients were also receiving immunomodulator therapies[122] ; anti-TNFα treated patients appeared to have an increased risk of lymphoma (SIR 3.23 95% CI 1.5-6.9) compared to the expected population rate[122]. The SIR was also increased when compared to previously studied patients on immunomodulator therapy alone (1.7 95% CI 0.5-7.1), however this did not reach statistical significance[122]. There were too few patients treated with isolated anti-TNF therapy to determine the individual risk of anti-TNF usage on lymphoma development[122].

Management principles in malignancy

The association between various malignancies and anti-TNF treatment remains unclear, but it is important that patients' history of previous or pre-existing cancer is carefully documented prior to initiation of biologic treatment. The use of biologics as monotherapy can be considered in patients with previous history of cancer. Axelrad et al noted that at 5 years after prior cancer diagnosis no significant difference in cancer free survival could be demonstrated between IBD treatment with anti-

TNF monotherapy, immunosuppressant monotherapy, anti-TNF combined with thiopurine therapy, though numerically anti-TNF monotherapy had the least cancer recurrence[123]. In a meta-analysis of 16 studies of immune mediated diseases, including 8 studies involving IBD patients, similar rates of cancer recurrence were observed among individuals affected by previous cancer who received no immunosuppressives, anti-TNF monotherapy, immunosuppressant therapy or combination therapies[124]. Therefore, in patients with a history of cancer, recent or past, effective therapy for IBD can be used after consideration of risks & benefits and discussion with oncologists. ECCO guidelines also provide advice on managing IBD patients with previous history of malignancy[125]. Generally, among biologics, monotherapy anti-TNFα, vedolizumab or ustekinumab may all be used, but often thiopurines are avoided.

Table 9- Malignancies with anti-TNF therapy

Complication	Causative drug/s	Diagnosis	Management Strategy
Melanoma	Anti-TNF	• Clinical diagnosis • Skin biopsy	1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Non-melanoma skin cancer	Dual Anti-TNF + thiopurine therapy	• Clinical diagnosis • Skin biopsy	1. Stop drug 2. Consider alternatives like Methotrexate or vedolizumab 3. Dermatology involvement
Lymphoma • **HSTCL** • **PTLD**	Dual Anti-TNF + thiopurine therapy	• Cross sectional imaging • Tissue Biopsy	1. Stop drug 2. Consider switching drug class
Other malignancies: Leukoencephalopathy	Dual Anti-TNF + thiopurine therapy	• Clinical diagnosis • Imaging • Tissue Biopsy	1. Stop the drug 2. Consider switching drug class 3. Relevant Specialist involvement

Anti – TNF : Anti-Tumour Necrosis Factor ; HSTCL: Hepatosplenic T-cell Lymphoma; PTLD: Post-transplant lymphoproliferative disorder

CONCLUSION

The use of biologics is now standard therapy for IBD used either as monotherapy or in combination with immunomodulators. A review of safety data of currently used biologics show cumulative evidence for anti-TNFα as they have been used for longer duration. In summary, acute infusion reactions are common with anti-TNF, neutropenia is a worrying AE and may require temporary cessation of therapy. Infections are significantly higher with anti-TNF which include common and uncommon bacterial infections, mycobacterial infections (in particular TB), viral and fungal infections and opportunistic pathogens. Diagnostic and management strategies are outlined in separate tables.

Anti-TNF therapy causes a wide range of dermatological presentations. It is important to differentiate drug induced psoriasis from psoriasiform rash. Treatment may range from topical therapy to anti-TNFα withdrawal. Ustekinumab may be useful in these cases.

Malignancies thought to be linked to anti-TNF use include solid organ malignancies, NMSC, melanoma, lymphoproliferative malignancies, and those with a viral association. However, difficulty remains in attributing a causal relationship particularly given the confounding of thiopurine use. The link between HSTCL is recognised but currently not quantified due to scarcity of data. IBD increases risk for NMSC, with the risk further increased for in combination therapy. The risk of lymphoma is increased with combination therapy with thiopurines including EBV related lymphoma but it is to be noted that results from the TREAT registry suggest that none of the immunosuppressants, infliximab or combination therapy are an independent risk factor for malignancy. However, the follow up duration remains short. Biologics can be used in patients with prior history of cancer after careful discussion about risks and benefits with oncologists.

Finally, although these therapies are often very effective, they present unique challenges. It is likely that in the future biologics will be used in a wider cohort of patients earlier in their disease journey, and therefore prompt recognition of adverse events secondary to drugs is important. Further reporting of rarer AEs and prompt recording of common AEs in registries will help assess risk more accurately. This information should help clinicians inform their patients of risks associated with each therapy and will lead to more informed decision making, thus improving patient care.

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