Risk of Infections of Biological Therapies with Accent on Inflammatory Bowel Disease

Radu M. Nanau1,2, Lawrence B. Cohen3,4 and Manuela G. Neuman1,2

1 Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, and 2 In Vitro Drug Safety and Biotechnology, 3 Division of Gastroenterology, Sunnybrook Health Science Centre, and 4 Departments of Internal Medicine, University of Toronto, Toronto, Ontario, Canada.

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ABSTRACT- Background: Biological therapies using anti-tumor necrosis factor (TNF)-α agents have an important impact in the treatment of inflammatory bowel disease, rheumatoid arthritis, psoriasis, and other inflammatory conditions. However, a significant number of patients lose their response to these medications over time. Clinical trials have demonstrated that antibodies against anti-TNF agents may impact treatment response and increase the risk of infusion reactions. Of concern is also the possibility of developing adverse events induced by anti-TNF agents. The purpose of the present systematic review is to describe the current knowledge on the risk of infections associated with anti-TNF agents antagonists, as well as integrin antagonists. We also intend to describe case reports of these adverse events in inflammatory bowel disease patients.

Methods: Currently approved anti-TNF biologicals in IBD include the monoclonal antibodies infliximab, adalimumab, certolizumab pegol and golimumab. Integrin antagonists include natalizumab, etrolizumab and vedolizumab.

Results: The most frequently-reported adverse events of these biologicals were infections, and these are described in detail in this study. Discussion: Most adverse events are due to the failure of host immunological control, which involves de novo infection, or reactivation of latent bacterial or viral infection, often with a different expression of disease. Conclusion: Risk assessment in individuals undergoing treatment with biologicals represents a step towards achieving treatment personalization to identify those patients that will safely benefit from this therapeutic approach. Patients and physicians must be alert for anti-TNF agents and anti-integrin medication as potential causes of drug-induced infections and monitor the therapies. Personalizing therapeutic vigilance promises to optimize benefits while minimizing infections.

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INTRODUCTION
The intermittent destructive inflammation of the intestinal tract describes a medical condition known as inflammatory bowel disease (IBD). The two main entities of IBD are Crohn’s disease (CD), histologically characterized by transmural inflammation with asymmetrical and discontinuous granulomas, and ulcerative colitis (UC), which can be identified through inflammation limited to the intestinal mucosa. A number of factors increase the risk of IBD, including genetic predisposition, and environmental and epigenetic factors. IBD was initially managed with agents such as 5-aminosalicylate formulations such as sulphasalazine, mesalamine and olsalazine, oral steroids such as prednisolone, methylprednisolone and budesonide, and immunomodulating drugs such as azathioprine, 6-mercaptopurine, cyclosporin and methotrexate (1, 2).

The development and pathogenesis of IBD is strongly mediated by inflammation, with tumor necrosis factor (TNF)-α, interferon (IFN) and interleukin (IL)-12/23 playing key roles (3, 4). As such, biological treatment with TNF-α inhibitors represents an important therapeutic strategy to block the pro-inflammatory cascade associated with this cytokine, thus re-establishing the balance between the pro- and anti-inflammatory messages.
Tumor necrosis factor-alpha (TNF-α) is a T helper 1 pro-inflammatory cytokine that plays a key role in the integrated host defence system against infectious diseases. This cytokine is physiologically antagonized by TNF-binding proteins (6). The four anti-TNF agents currently approved in IBD are the monoclonal antibodies infliximab (IFX; Remicade), adalimumab (ADM; Humira), certolizumab pegol (CZP; Cimzia) and golimumab (GLM; Simponi). Due to its lack of efficacy in active CD, the anti-TNF fusion protein etanercept (Enbrel) is not used (7). In addition, integrin antagonists such as natalizumab (NTZ; Tysabri), vedolizumab (VDZ; Entyvio) and etrolizumab (ETZ, Genentech Inc.) have also been used.

As immunomodulatory therapies, anti-TNF agents lower the ability of the immune system to ward off infections. Serious infections are the primary adverse events associated with biological therapies (8). These include tuberculosis (TB) and infections caused by other bacteria, fungi and viruses that have spread throughout the body, especially among older individuals (9-12). As IBD patients account for one third of biologicals users (13), it is important to understand the adverse events associated with their use in this population. Moreover, this knowledge will impact on the personalized medication and ultimately in patients health.

Integrins are involved in the adhesion of leukocytes to the vascular endothelium, and their migration from the circulation into the inflamed tissue. Integrins also contribute to the activation of immune cells through molecular signalling (14). These glycoproteins bind matrix proteins in the intestinal mucosa, as well as ligands such as intercellular adhesion molecules and vascular cell adhesion molecule-1 (15). Their role in the inflammation and repair of the intestinal mucosa was described by Jones et al. (16) and reviewed by Gosh et al. (17).

The incidence of serious infections was 2.2% in a large IBD sample treated with anti-TNF agents over an 11 years period in Australia and New Zealand (18). Cases of active TB were prevented by administering prophylaxis prior to initiating anti-TNF treatment in individuals with latent TB (18). Non-TB opportunistic infections identified in the French research axed on tolerance of biotherapies registry and in the Australian and New Zealand cohort include bacterial infections such as non-TB mycobacteriosis (NTM), listeriosis, nocardiosis, salmonellosis and staphylococcosis, fungal infections such as pneumocystosis, aspergillosis and cryptococcosis, and viral infections such as cytomegalovirus (CMV), varicella zoster virus (VZV) and herpes simplex virus (HSV) (18, 19). IFX treatment [odds ratio (OR) 10.9, 95% confidence interval (CI) 2.9-40.8, p=0.0004] and ADM treatment (OR 6.1, 95% CI 1.5-25.5, p=0.013) were risk factors for opportunistic infections in a case-control analysis of patients treated with anti-TNF agents (19). Concomitant immunosuppressant treatment, particularly steroids, is an additional risk factor for opportunistic infections (19-21). In a large review, the highest risk of opportunistic infections was among CD patients undergoing anti-TNF treatment with concomitant steroids compared to individuals without CD (OR 14.09, 95% CI 2.84-69.81), showing that a diagnosis of CD, anti-TNF treatment and especially immunosuppressant combinations are risk factors for opportunistic infections (20).

The most common infections associated with IFX affect the respiratory (including sinusitis, pharyngitis and bronchitis) and the urinary tracts. Serious infections including TB, pneumonia, cellulitis, abscess, skin ulceration and sepsis are rare in IBD patients undergoing anti-TNF treatment (9). Upper respiratory tract infections were also the most common infectious adverse events in pediatric IBD patients treated with IFX, along with lower respiratory tract infections, skin and soft tissue infections, gastrointestinal infections, musculoskeletal infections, genitourinary infections, and well as sepsis/bacteremia, meningitis, histoplasmosis and Mycobacterium infections (including both pulmonary and extrapulmonary TB) (22-25). The most common opportunistic infections in children and adolescents are caused by viruses, including primary VZV, herpes zoster, HSV and Epstein-Barr virus (EBV) (25). As these infections are largely limited to members of the herpesvirus family, which are generally acquired during childhood, it is unclear whether their acquisition relates to the underlying disease or to the anti-TNF treatment. Rare fungal and bacterial infections, including pulmonary TB, are likely to be related to intrinsic factors and to immunosuppression (25). The overall rates of infections were similar between UC and CD patients (22, 24).
The rates of serious infections are generally similar between IFX regimens and placebo (26). A large review found comparable rates of developing opportunistic infections between CD patients receiving anti-TNF treatment alone and CD patients not receiving any treatment (20). There were no significant differences in the rates of serious infections requiring treatment modifications between patients who received one or multiple IFX infusions (27). The incidence of opportunistic infections was highest during the first year of IFX treatment in a retrospective cohort. Previous treatment with ≥2 immunosuppressive agents was the main risk for developing opportunistic infections while receiving IFX. Severe infection rates are higher in elderly IBD patients (≥65 years) treated with IFX or ADM compared to elderly IBD patients (≥65 years) treated with non-biologicals or younger IBD patients (<65 years) treated with IFX or ADM (28).

The most serious adverse events of ADM are also infections, including new onset and reactivation of TB, with both pulmonary and extrapulmonary manifestations, as well as other previous infections with bacteria, invasive fungi, viruses, parasites (10). The rates of infection were similar between ADM and placebo patients, regardless of presence of immunosuppressants (29). A separate trial found infections to be more common in ADM patients during the maintenance phase compared to the induction phase (30).

Less information is available for CZP and GLM. Acquiring or worsening pre-existing infections is the main type of adverse event associated with CZP (11). The rates of adverse events, including infections, were similar between CZP and placebo in CD patients, both in the short term and in the long term (31, 32). GLM is similarly associated with serious infections, the most notable of which are TB and hepatitis B virus (HBV) reactivation, but also sepsis, pneumonia, cellulitis, abscess and invasive fungal infections (12, 33, 34). Serious infections were reported in 3.2% of patients with moderate to severe UC receiving GLM (34). The rates of infection were similar between GLM and placebo in the short term (33). Despite low incidences of infections in either group, GLM may be associated with a higher risk in the long term (34). The incidence of TB through week 54 was similar between GLM and placebo (34).

Due to the increased risk of serious infections associated with anti-TNF treatment (9-12), adherence to several guidelines can help lead to a safer anti-TNF treatment course in gastroenterology, rheumatology and dermatology patients (38). Screening for active or latent TB is strongly recommended. On the other hand, screening for CMV or EBV is not necessary, nor is it necessary for hepatitis C virus (HCV). Vaccination against VZV and annual influenza vaccine are recommended. Vaccination against HBV is also recommended, although its efficiency in preventing HBV infection remains debatable in patients undergoing anti-TNF treatment. Vaccination against human papilloma virus is recommended in the general young female population, with an unclear relationship between anti-TNF treatment and the efficacy of vaccination. Anti-TNF treatment is generally not considered to increase human immunodeficiency virus (HIV) viremia (38).

The present systematic review aims to identify and describe infectious adverse events associated with the use of anti-TNF agents and integrin antagonists, with a particular focus on patients afflicted with IBD. The various microorganisms responsible for the infections were identified in clinical trials and cohort studies, while case reports described in detail the clinical manifestations and disease course of these infections.

**MATERIALS AND METHODS**

Placebo-controlled trials assessing the efficacy and safety of IFX, ADM, CZP and GLM in IBD patients were identified through a PubMed search using combination of terms with the name of the drug ("infliximab," "adalimumab," "certolizumab pegol," "golimumab," "natalizumab," "vedolizumab" and "etrolizumab"), the name of the disease ("Crohn’s disease," "ulcerative colitis" or "inflammatory bowel disease"), and the term "clinical trial." Recent open-label trials (2010-2014) were also retrieved using similar search criteria. The risk of infection was further assessed in other recent cohort studies, especially ones involving IBD patients, using the name of the drug and one of "tuberculosis,” “Mycobacterium,” “listeriosis,”
"Listeria," "legionellosis," "Legionella," "staphylococccemia," "Staphylococcus," "salmonellosis," "Salmonella," "nocardiosis," "Nocardia," "Pseudomonas," "pneumocystosis," "Pneumocystis," "histoplasmosis," "Histoplasma," "aspergillus," "Aspergillus," "cryptococcosis," "Cryptococcus," "candidiasis," "Candida," "actinomycosis," "Actinomyces," "blastozyomycosis," "Blastozyomes," "coccidiodosis," "Coccidioides," "hepatitis B virus," "hepatitis C virus," "herpesvirus," "cytomegalivirus," "varicella zoster virus," "herpes simplex virus," "Epstein-Barr virus," "John Cunningham virus" and "human immunodeficiency virus." Case reports describing these infections in IBD patients were reviewed regardless of when they were published. An additional Google Scholar search was performed. Nevertheless, there are interpretation limitations since data collection by various centers may introduce great variability. Moreover, there is patient heterogeneity depending on the criteria of the study, as well as the variants taken into account in each study. We have to acknowledge that this is a systematic review of the literature, but no meta-analysis of the data was carried out.

RESULTS AND DISCUSSIONS

BACTERIAL INFECTIONS

Tuberculosis

TB is an infectious disease caused by Mycobacterium tuberculosis. De novo TB infections or reactivation of latent TB infections are the adverse events of most concern in patients with inflammatory diseases undergoing anti-TNF treatment. In the French research axed on tolerance of biotherapies registry, the rate of TB was higher among anti-TNF patients than among the general population (standardized incidence ratio (SIR) 12.2, 95% CI 9.7-15.5 for anti-TNF treatment, SIR 18.6, 95% CI 13.4-25.8 for IFX and SIR 29.3 95% CI 20.2-42.4 for ADM) (39). Similar findings are reported elsewhere (40, 41). The incidence of TB was 3.3% among patients with inflammatory diseases in a Portuguese population (41). TB occurs predominantly in the first 6 months of treatment with anti-TNF agents (42).

The risk of serious infections differs between anti-TNF biologicals according to the drug class. The rates of TB are higher in patients receiving monoclonal antibodies (IFX and ADM). An in vitro study using peripheral blood mononuclear cells stimulated with M. tuberculosis antigen showed that IFX almost completely abolishes TNF-α release, while also reducing IFN-γ release. This has important implications as TNF-α and IFN-γ contribute to the formation of granulomas and the containment of bacteria (43). Significantly, anti-TNF monoclonal antibodies suppress IFN-γ production by IL-10-independent mechanisms. IFX and ADM interfere with immune functions mediated by TNF-α, leading to inadequate maturation and acidification of mycobacteria-containing phagosomes, as well as decreased autophagy and apoptosis of mycobacteria-containing macrophages. This further interferes with mycobacteria antigen presentation and innate immunity. As such, monoclonal antibodies suppress antigen-induced IFN-γ production. IFX and ADM thus have concentration-dependent effects on the control of intracellular growth of M. tuberculosis (44-48).

IFX was also linked with complement-mediated lysis of cells expressing transmembrane TNF-α, such as macrophages and monocytes. Mechanistically, the loss of macrophages and monocytes leads to a shift towards proliferation of immunosuppressive regulatory T cells, leading to overall increased IL-10 release and diminished IFN-γ production. IL-10 itself increases the susceptibility of TB reactivation, as it allows M. tuberculosis to evade immune responses (48- 52).

The same properties that make monoclonal antibodies efficacious in granulomatous diseases such as CD also increase the susceptibility to granulomatous infections like TB. Latent TB is characterized by the presence of granulomas sequestering the bacillus, preventing its multiplying and dissemination. The TNF-mediated formation and maintenance of bacteria-containing granulomas is essential for M. tuberculosis infection control, and anti-TNF monoclonal antibodies compromise the integrity of bacteria-containing granulomas (47, 48, 53-55).

Due to the key role played by TNF-α in preventing TB reactivation, screening for latent TB consisting of detailed medical history, chest X-ray, and laboratory tests that evaluate immunologic responses to the presence of M. tuberculosis is recommended in patients requiring anti-TNF treatment. Some of the most common tests are the tuberculin skin test (TST) and an IFN-γ release...
assay such as the QuantiFERON-TB Gold test (QFT-G). The concomitant use of IFN-γ release assays and TST is recommended in pediatric patients. Prophylactic treatment is recommended in all patients with persistent *M. tuberculosis* immune responses prior to initiating anti-TNF treatment (56-58). On the other hand, a normal chest radiograph prior to anti-TNF treatment is a poor predictor of future active TB development (59, 60).

The TST, also known as purified protein derivative or Mantoux test, is a screening tool for latent TB infection, in which tuberculin, an extract of *M. tuberculosis*, is injected intradermally and the immune response in the skin is measured after 48-72 h. A TST of ≥5 mm among patients receiving immunosuppressive treatment is considered positive, and treatment for latent TB is recommended. A positive TST was observed in 20.2% of an IBD cohort from a Brazilian region with a high endemic TB rate, and these were similar to the general local population (54). In contrast, latent TB infection was positive in 7.0% of IBD patients undergoing anti-TNF treatment at a hospital in Spain over a 12 years period based on TST and chest X-ray (61). In another Spanish IBD sample undergoing long-term IFX or ADM treatment, a low TST conversion rate of 2.7% was observed in patients with negative baseline latent TB infection (62). The rate of TB was 0.2% in a Northern California sample of anti-TNF users over a 9 years period, corresponding to 49 cases per 100000 person-years (63). The absence of TB in another large American CD sample treated with IFX reflects its low endemic rate in this setting, estimated at 2.8 cases per 100000 person-years in the general population (64).

IFN-γ release assays measure IFN-γ release in blood by TB-specific effector T cells. These assays provide greater specificity and possibly greater sensitivity than TST (65). The usefulness of TB screening was assessed in IBD patients receiving anti-TNF treatment with baseline tests negative for latent TB in Spain. Chemoprophylaxis with isoniazid without discontinuation of anti-TNF treatment prevented active TB in all patients showing conversion by TST. IFN-γ release assays produced persistently negative results in these patients. The disagreement between the tests suggests previous infection followed by antigen clearance, resulting in a lack of IFN-γ production (62). Among two patients with a positive TST and negative QFT-G assay in another study, one was treated for TB during childhood, while the other received isoniazid prophylaxis, and both did well on ADM (66).

With a TST negative predictive value of 95.8% among immunocompromised patients and 100% among immunocompetent patients, it is highly advantageous to perform such assays prior to commencing immunosuppressive treatment (67). Periodic retesting is also encouraged in patients with initially negative results. While undergoing anti-TNF treatment, 7 patients developed TB in a study (1.6% of the sample), of which only 1 tested positive for latent TB infection (61). False negative TST or IFN-γ release assay results increase the risk of TB reactivation in chronic inflammatory disease patients receiving anti-TNF treatment (67).

TB prophylaxis administered prior to commencing anti-TNF treatment generally prevents the development of active TB (61). In a real life IBD cohort treated with anti-TNF agents, the rate of QFT-G assay positivity was 1.5% (5 of 340 patients). Of 4 patients identified prior to anti-TNF treatment (two positive for TST, one untested and one negative), three received prophylactic TB treatment and showed no signs of active TB when exposed to anti-TNF treatment. The fourth patient was considered low risk due to negative TST and normal chest X-ray, and developed no pulmonary symptoms while on ADM. A fifth patient was positive for QFT-G while on ADM and was referred to an infectious diseases clinic (66).

Chen et al. (68) report two patterns of TB active disease in anti-TNF patients, the first of which involves the reactivation of latent TB infection in patients with positive QFT-G assay results, usually in the first 3 months of anti-TNF treatment. The second pattern involves TB infection in patients with initially negative QFT-G assay and TST, usually after ≥2 years of anti-TNF treatment. This biphasic pattern of active TB emphasizes the risk of TB infection in anti-TNF patients, despite an initially negative screen at the start of treatment (68). *De novo* contamination was observed in patients receiving anti-TNF treatment when coming into contact with infected individuals or traveling to regions with high endemic TB rates (59, 66). Travel to or immigration from areas with a high endemic TB rate may explain some cases diagnosed in areas with a low endemic rate (61). Among patients born in regions with low endemic TB rates, being a
healthcare worker might be a risk factor of contacting the disease (60).

No gender differences were found with respect to the development of TB (40). In case-control comparisons, using controls with community-acquired TB, disease outcomes and treatment strategies were similar (41). However, TB reactivation during anti-TNF treatment generally follows an abnormal disease course. While pulmonary manifestations are more predominant in controls, anti-TNF treatment patients often experience extra-pulmonary disseminations, suggesting poor disease control by the host (41, 48, 49). Of 7 patients who developed TB in a study, 5 were receiving concomitant immunosuppressants (61).

The most common risk factors for IFX-induced TB in a large series of 130 cases submitted to the US Food and Drug Administration (FDA) between 2001 and 2006 include the concomitant use of immunosuppressants (68.4%), a history of latent TB (25.4%) and being born into or having spent extensive time in a TB endemic area (19.2%), as well as diabetes and chronic renal disease (63, 69). As these represent spontaneous reports, the accuracy of these results may in fact be low (69). TB restricted to the lungs was reported in 36.9% of cases and extra-pulmonary TB in 45.4% of cases. Among patients with extra-pulmonary manifestations, disseminated disease was reported in 52.5% of cases (23.8% of total), with others affected by peritoneal disease, lymph node disease, bone or joint disease, enteric disease, meningeal disease, hepatic disease, pericardial disease or pelvic disease. Hospitalization was required in 51.5% of cases, with 14.6% being fatal (69).

Table 1 summarizes case reports of active TB in IBD patients undergoing anti-TNF treatment. Common manifestations of TB at the time of hospitalization include fever, fatigue, weakness, weight loss, dry cough, diarrhea and vomiting (70-81). Another common manifestation is systemic inflammation, exemplified by elevated C-reactive protein (CRP) levels (72, 74, 76, 77, 80). Abdominal pain and tenderness have also been reported (74, 76, 80).

Other manifestations depend largely on the organs affected, which may include the lungs, liver, spleen, brain, peritoneal cavity and joints. Cases presenting solely with pulmonary manifestations generally have an uncomplicated disease course (70, 71). Mediastinal adenopathy accompanied pulmonary TB in another case (72). A case of thoracic TB disseminated to the lungs was characterized by widened mediastinum (73). Several cases show pulmonary TB with concomitant liver or spleen involvement. Pulmonary TB with nodular lesions in the liver and spleen is described in one case (74), while pulmonary nodules accompany a case of hepatosplenic TB (75). Micronodular spleen lesions (76), hepatosplenomegaly with micronodular spleen lesions (77) and hepatic cytolysis with bone marrow involvement (78) accompanied three cases with miliary pattern and lymphatic involvement. Miliary TB was accompanied by monoarthritis in another case (79). A rare case of disseminated TB involving the brain with cerebral tuberculomas, and pulmonary, lymphatic and skin manifestations is also described (78). Primary tuberculous peritonitis without lung involvement was diagnosed in another patient (80). A case of anal TB showed a persistent anal ulcer (81). Additional cases of pulmonary and extrapulmonary TB, including renal, nodal and peritoneal TB are also reported in a single center study over a period of 12 years (61).

The late diagnosis of active TB can lead to delayed treatment and bacterial clearance, and a more complicated disease course (77, 80). Several other cases of TB were identified as adverse events in patients treated with IFX, ADM, CZP and GLM in clinical trials. These cases are not presented in detail (26, 29, 32, 34, 82, 83). A case of fatal TB occurred in a patient treated with GLM who tested positive for latent TB infection and received isoniazid prophylaxis (34).

In several cases, worsening of pre-existing TB, a phenomenon known as paradoxical reaction, occurs after initial symptoms improvement (71, 72, 74, 76, 81). Lymphadenopathy is the most common manifestation of paradoxical reaction (71, 72, 74, 76, 81). The initial symptoms of fever, worsening of fatigue, cough, weight loss and inflammation return (71, 74). Bacterial cultures are generally negative, suggesting clearance of the infectious microorganism (81). Paradoxical reactions occur as a result of immune reconstitution inflammatory syndrome upon discontinuation of immunosuppressants such as anti-TNF treatment (72, 76).
Non-tuberculous Mycobacterial Diseases
The rate of NTM, also known as environmental mycobacteriosis, was 0.2% in a Northern California sample of anti-TNF users over a 9 years period, corresponding to 74 cases per 100000 person-years overall, and 116 and 122 cases per 100000 person-years among IFX and ADM patients, respectively. Background rates of NTM of 4.1 cases per 100000 person-years are reported in the general American population (63). Mycobacterium avium, rapid growing Mycobacteria and Mycobacterium marinum were the most frequently reported NTMs among anti-TNF patients in the US FDA MedWatch database (84). Older age was the main risk factor for NTM (63). NTMs in IBD patients receiving anti-TNF treatment include M. marinum and M. avium, both of which are free-living microorganisms causing opportunistic infections in humans, particularly immunocompromised individuals. Case reports are presented in Table 2 (85-92).

IBD patients who develop M. marinum generally present cutaneous manifestations around an injury site. Most M. marinum infections result from exposure to sea water or aquatic animals. Sources of M. marinum include fishes and fish tanks (85, 86, 89, 90), as well as recent trips to tropical seas (87, 88). Manifestations of cutaneous M. marinum infections can include erythematous, papular or scaly skin lesions (85-88, 90), often accompanied by subcutaneous nodules (85-87, 89, 90) and inflammation with slightly elevated CRP levels (85, 87-90). Microscopic examination of dense skin biopsies reveal lymphohistiocytic infiltrate and granulomatous inflammation (87, 89). A sporotrichoid pattern is sometimes reported (88-90).

Two cases of M. avium complex infection are described, with a pulmonary presentation in one (91) and lymphadenopathy in the other (92). Immune reconstitution inflammatory syndrome worsened the course of the first (91). M. avium complex infection is reported in another CD patient treated with IFX in a cohort study (64).

Listeria monocytogenes
Listeriosis is a common bacterial infection caused primarily by Listeria monocytogenes, a virulent food-borne pathogen that affects pregnant women and old or immunocompromised individuals. Based on data from the FDA Adverse Event Reporting System, 38% of L. monocytogenes infections attributed to biologics occurred in IBD patients. Listeriosis was most common in IFX patients with concomitant immunosuppressive treatment (93). L. monocytogenes infections in IBD patients treated with IFX or ADM are detailed in several case reports reviewed in Table 2 (94-106).

The estimated L. monocytogenes infection rate was 43 cases per 100000 persons treated with IFX compared to 3 cases per 100000 persons in the general American population, based on data from the FDA and the Centers for Disease Control and Prevention Emerging Infections Program (104). In a more recent report, the incidence of L. monocytogenes infection was 0.256 (95% CI 0.115-0.570) per 1000 patient-years in the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases. This was higher than the 0.0034 per 1000 person-years incidence in the general European population, giving rise to a risk ratio of 75.3 (95% CI 33.8-168.0, p<0.001) of developing L. monocytogenes infection for RA patients undergoing anti-TNF treatment (107). Davies et al. (108) found that the inclusion of dietary warnings about the risk of Listeria and Salmonella infections in the product information of anti-TNF biologics led to a significant reduction in the rate of infections with these bacteria in a cohort of RA patients.

The main clinical presentations of L. monocytogenes infections are sepsis and meningitis. Almost all cases present sepsis, diagnosed by the ability to culture L. monocytogenes in blood samples (94-106), with the rest showing L. monocytogenes growth from cerebrospinal fluid (CSF) (104-106). Meningitis was diagnosed in several cases (99-106). Another case of L. monocytogenes meningitis is reported in a CD patient treated with IFX in a cohort study (109). Three additional cases of L. monocytogenes infection were reported in CD patients treated with IFX, 2 of which developed meningitis. Meningitis was fatal in one of these cases, while it led to permanent eye paralysis in the other (104).

Symptoms were similar regardless of whether L. monocytogenes could be cultured in blood, CSF or both, and included weakness, lethargy, fever, diarrhea, abdominal pain, anorexia, malaise, hypotension, nausea and emesis, and diaphoresis. Inflammation with leukocytosis and/or elevated CRP is the predominant feature of L.
monocytogenes infection (94-106). In addition, symptoms such as headache, neck stiffness, rigors, dizziness, confusion, disorientation, delirium and meningeal irritation were noted in cases involving meningitis (97, 99-106). Splenic abscesses developed in one case (95), and slightly elevated liver transaminases were observed in another case (105). In several cases, cloudy CSF with increased levels of protein and/or leukocytosis was also noted (97, 101, 103, 105, 106).

The disease course was complicated by fungal sepsis with Candida albicans in one report (99). Oftentimes, the source of infection is unclear. For example, ingestion of processed meats is reported in one case (94), while no history of having eaten anything suspicious is noted in others (99, 102). No mention is made in the remaining cases. Co-infection with HIV, which is a risk factor for acquiring Listeria infection, is reported in one patient. The effects of the co-infection on the course of either disease are unknown, as HIV viremia was undetectable and the CD4+ cells counts exceeded 350/mm³ at the time of the bacterial infection (103).

Legionella pneumophila
Legionella pneumophila is an intracellular gram-negative bacterium that is a significant cause of community-acquired pneumonia. L. pneumophila pneumonia can further advance to a severe condition known as legionellosis or Legionnaires' disease (110). The incidence of legionellosis among anti-TNF patients reported in the French research axed on tolerance of biotherapies registry was 46.7 (95% CI 0.0-125.7) per 100000 patient-years over a 4 years period compared to 2.3 per 100000 patient-years in the general French population (OR 13.1, 95% CI 9.0-19.1, p<0.0001). Adjusted to the risk of developing legionellosis in the general French population, IFX (OR 15.3, 95% CI 8.5-27.6, p<0.0001) and ADM (OR 37.7, 95% CI 21.9-64.9, p<0.0001) represent risk factors (110). This is comparable with an earlier report from the same population that saw a 16.5-21-fold higher incidence of L. pneumophila among anti-TNF patients compared to the general French population. As such, legionellosis should be considered in anti-TNF patients presenting pneumonia (39).

L. pneumophila infections are detailed in a few case reports in IBD patients treated with IFX, summarized in Table 2 (111-115). L. pneumophila pneumonia is also reported in a CD patient treated with ADM in an open-label clinical study (116). Symptoms of L. pneumophila pneumonia include fever, cough, and fatigue leading to syncope (113-115). Respiratory insufficiency progressing to respiratory failure may also develop (113, 114). Inflammation with elevated CRP levels and leukocytosis is further reported (113, 115), progressing to pulmonary consolidation in one case (115). Other pulmonary symptoms include tachypnea (114), as well as pulmonary infiltrates that progressed to abscess (112-114). Stethoscopic findings such as rales were also common (113-115). A lung biopsy belonging to a patient with L. pneumophila pneumonia grew CMV, yet the implications of the co-infection with this virus are not detailed (114). Interestingly, in one case, the source of infection was identified as community-acquired legionellosis, as L. pneumophila was cultured from water collected in the patient’s shower (113).

Staphylococcus aureus
Staphylococcus aureus is a bacterium frequently found in the human respiratory tract and on the skin. Pathogenic S. aureus infections are described in Table 2 in several IBD patients treated with IFX. A case of S. aureus infection also occurred in a UC patient treated with GLM in a recent clinical trial (34). Manifestations of S. aureus infections were varied.

Skin lesions, adult respiratory distress syndrome and severe sepsis were diagnosed in a patient. Symptoms included fever, dyspnea, coughing and elevated CRP levels, as well as renal failure. Hyperventilation with severe hypoxemia and acidosis, and large pneumonic infiltrates exemplify the pulmonary symptoms (117). Septic arthritis was diagnosed in two patients. Staphylococcal osteomyelitis masked an osseous mycobacterial infection in one patient (118), while septic arthritis and lumbar empyema were diagnosed in a patient with severe polyarthalgias, leukocytosis and elevated CRP levels (119). A subretinal abscess with bacterial endophthalmitis caused by an intraocular cilium presented as blurred vision, pain, inflammation and vitreous opacity (120). Fever, severe inflammation with leukocytosis and elevated CRP levels, elevated aspartate transferase (AST) of 87 IU/L and alanine transferase (ALT) of 149 IU/L, and heterogeneous liver lesions preceded a liver abscess (121).
Other Bacterial Infections

*Neisseria meningitidis* is another bacterium associated with meningitis. A patient diagnosed with *Neisseria meningitidis* meningitis presented with fever, agitation, altered sensorium, nuchal rigidity and leukocytosis in CSF (122). *Nocardia* infections manifest as either cutaneous nocardiosis or *Nocardia* pneumonia in CD patients treated with IFX. Case reports are detailed in Table 2. Symptoms of cutaneous nocardiosis included erythematous papulopustular lesions in one patient (123) and papules progressing to skin abscess in another (124). Two cases of *Nocardia* pneumonia show fever, chest pain, dyspnea, cough, tachypnea and inflammation, as well as pulmonary crackles and pulmonary consolidation (125, 126). A case of *Nocardia* infection also occurred in a UC patient treated with GLM in a recent clinical trial (34).

Two cases of *Pseudomonas aeruginosa* pneumonia occurred in UC patients treated with IFX in cohort studies (127, 128). *P. aeruginosa* and *Enterococcus* species were also cultured in a patient with *L. pneumophila* pneumonia (114).

One case of septic arthritis with *Salmonella enteritidis* and two cases of sepsis with *Salmonella typhimurium* and *Salmonella enterica* manifested as fever, abdominal pain, leukocytosis and elevated CRP levels (129-131). Another case of *Salmonella enterica* infection, starting as urosepsis, led to the development of acute renal failure, acidosis and respiratory failure (132).

The incidence of *Clostridium difficile* colitis was 28.6% in a small sample pediatric of CD patients undergoing concomitant methotrexate and anti-TNF-a treatment. This led to complicated disease course and increased the odds of treatment failure (133). While concomitant corticosteroids were a risk factor for *Clostridium difficile* infections in IBD patients treated with IFX, IFX alone did not increase the chance of acquiring this type of bacterial infections (134).

OPPORTUNISTIC FUNGAL INFECTIONS

*Pneumocystis jirovecii*

Pneumocystosis was the most common non-viral opportunistic infection in a large cohort of new anti-TNF patients suffering from IBD or autoimmune diseases (21). In a review of the FDA Adverse Event Reporting System database, 84 cases of *Pneumocystis jirovecii* pneumonia were identified over a period of 6 years among patients treated with IFX for various conditions including CD, UC, RA, ankylosing spondylitis and psoriatic arthritis (135). Concomitant exposure to immunosuppressants and IFX for a duration of >3 years are the main risk factors for *P. jirovecii* colonization (135, 136). The onset of pneumonia generally occurs after a mean 21 ± 18 days since starting IFX, or a mean 2.1 ± 1.3 IFX infusions (135). *P. jirovecii* pneumonia results in death in over one quarter of cases (135).

Case report of *P. jirovecii* infection are detailed in Table 3 (137-144). Symptoms of *P. jirovecii* pneumonia include fever, cough, fatigue, nausea, diarrhea, abdominal tenderness and pain, and deteriorating respiratory status with dyspnea and tachypnea, occasionally progressing to respiratory failure (137-144). Other pulmonary manifestations encompass pulmonary rales, pulmonary opacity, interstitial infiltrates consistent with pneumonia, as well as pulmonary microabscess (138-144). Inflammation with elevated CRP was observed in some cases (138, 141, 143). Leukopenia was also a common feature (138, 141, 143, 144). In contrast, leukocytosis was reported in a case with concomitant pulmonary *Nocardia asteroides* infection (140).

*Histoplasma capsulatum*

*Histoplasma capsulatum* is the most common fungal infection in the US. Opportunistic infections with this microorganism are most common around the valleys of the Ohio and Mississippi rivers (9, 10). Opportunistic *H. capsulatum* infections affect primarily the lungs. Case reports in IBD patients are described in Table 3 (145-149).

Common symptoms of *H. capsulatum* infections include fever, fatigue, chills, night sweats, malaise, dizziness, nausea, poor appetite followed by anorexia and weight loss, abdominal pain, headaches, muscle aches, joint pain, as well as coughing and dyspnea (145-149). The most common pulmonary manifestations are nodules and opacities consistent with interstitial pneumonia (145-147). Disseminated histoplasmosis is often accompanied by lymphadenopathy (146, 147). Diffuse alveolar infiltrates were shown by chest X ray, and granuloma consisting of nodules of epithelioid histiocytes and lymphocytes were shown by biopsy in one patient (148).

Other cases of disseminated histoplasmosis include one case with anus involvement with necrotizing perianal soft tissue infection and pain,
fibrotic inflammation, perianal fissure and focal abscess (145), hepatosplenomegaly with elevated inflammatory markers, mildly elevated transaminases and elevated lactate dehydrogenase, and concomitant Pneumocystis pneumonia (146), and a case of edematous and erythematous epiglottis, with odynophagia, hoarseness and an exophytic lesion (149).

Reactivation of histoplasmosis was suspected in two patients previously exposed to a histoplasmosis pandemic (144, 148). A case of fatal Histoplasma pneumonia is reported in a UC patient treated with IFX in a large study (26).

**Aspergillosis**

Aspergillus fumigatus represents another common fungal infection in immunocompromised individuals. Four cases of aspergillosis are described in CD patients, with three fatalities and one unknown outcome in a patient lost to follow-up (150-153). Fever, cough, dyspnea, leukocytosis and elevated CRP levels, as well as pulmonary infiltrates and respiratory insufficiency are reported in two cases of fatal aspergillosis (150, 151). Fatal disseminated A. fumigatus involving multiple organs is chronicled in a patient who developed dyspnea, respiratory insufficiency, and pulmonary infiltrates and opacities, followed by pericarditis, ischemic injury and multiorgan failure (152). Concomitant Nocardia brasiliensis, A. fumigatus and A. niger infections are described in a patient presenting with cough, abdominal pain, elevated CRP and pulmonary nodular lesions (153).

**Cryptococcus neoformans**

Asymptomatic pulmonary cryptococcosis was identified in two patients during hospitalization for CD-related medical procedures (154, 155). No respiratory symptoms were present. Pulmonary nodules without lymphadenopathy were noted by chest CT scan (154, 155). A case of possible pulmonary cryptococcosis with fever, elevated CRP, and pulmonary nodules and infiltration is reported elsewhere (156). Two cases of pulmonary Cryptococcus neoformans infection, with initial presentations of fever, night sweats, headache, chest and abdominal pain, cough and dyspnea are reported in a CD patient treated with IFX and a CD patient with concomitant ankylosing spondylitis treated with ADM (157, 158). The first patient developed slightly elevated liver transaminases and pulmonary nodules, as well as a linear ulcer near the terminal ileum not consistent with CD exacerbation, with the additional colitis symptoms likely related to the fungal infection. Further dissemination to CSF without neurological symptoms was noted (157). Pulmonary opacities and crackles, as well as lymphadenopathy, are reported in the second patient (158). Cryptococcosis was speculated to be related to recent contact with poultry or pigeons in two patients (155, 158).

**Candidiasis**

Candidiasis encompasses the entire spectrum of infections caused by fungi of the Candida genus. Disseminated candidiasis attributed to C. glabrata is described in a CD patient treated with IFX (159). The disease course started off with fever. A granulomatous pulmonary lesion was first identified, followed by pulmonary nodules, alveolar condensations, bilateral pleural effusion and slightly elevated bilirubin and transaminases (159).

Fungal sepsis with C. albicans further complicated the clinical course of a previously described case of Listeria meningitis (99). Catheter-related C. parapsilosis was detected in a patient during treatment for methicillin-resistant S. aureus. Successful treatment of this fungal infection did not affect the disease course or the treatment of the previously identified bacterial infection (121). Catheter-related candidemia was also identified in a patient with Legionella pneumonia (114).

Co-infection with C. albicans led to an oropharyngeal infection in a patient with P. jirovecii pneumonia, as well as pulmonary infection with Nocardia spp. This patient was further afflicted by a urinary tract infection associated with Proteus mirabilis and airways infection associated with Acinetobacter baumanii (140). Oral infection with C. albicans that did not necessitate treatment was observed in another patient with P. jirovecii pneumonia (139). Co-infection with Candida species was detected in a patient who died from multiorgan failure due to aspergillosis (152).

Oral candidiasis was a non-serious opportunistic infection in a CD patient receiving open-label ADM (116). Esophagitis and vaginitis secondary to Candida were identified as important infectious adverse events in CD patients treated with ADM in clinical practice (83). Esophageal candidiasis was also identified as an opportunistic infection in randomized, placebo-controlled studies
of UC patients treated with ADM or GLM (33, 160).

**Other Opportunistic Fungal Infections**

A pulmonary infection with *Actinomyces graevenitzii* manifesting as fever, night sweats and cough, along with pulmonary crackles, consolidation and opacity is described in a CD patient treated with IFX (161). Malaise, fatigue, night sweats and cough, along with pulmonary crackles and infiltrate were noted in a UC patient treated with IFX who developed *Blastomyces dermatitidis* (162).

Disseminated *Coccidioides immitis* with meningeal, bone, soft tissue and pulmonary involvement was fatal in a CD patient treated with ADM. The disease further involved splenic granulomatous nodules, pulmonary nodules and multinodular thyroid disease. Lymphadenopathy, erythematous skin lesions, joint inflammation with soft tissue swelling, elevated liver transaminases, splenomegaly, bilateral infiltrates, and pleural effusion were identified subsequently. A brain magnetic resonance imaging revealed focal fluid-attenuated inversion recovery hyperintensities and nodular foci in the cerebral white matter. The patient also developed acute renal insufficiency, and eventually died due to the numerous manifestations of disseminated coccidioidomycosis (163).

**VIRAL INFECTIONS**

**Hepatitis B Virus Reactivation**

The main viral infection associated with anti-TNF treatment in IBD patients is HBV, particularly reactivation of latent HBV. Since TNF-α suppresses viral replication, TNF-α inhibitors may lead to HBV reactivation. While IFX is associated with a greater incidence of HBV reactivation than ADM, screening for chronic HBV infection with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) is recommended in all patients prior to initiating anti-TNF treatment. Viral replication can be reduced by treatment with antiviral therapy (164).

The HBV infection status is classified based on the serological assessment of several HBV-specific antigens and antibodies. The specific combination of biomarkers denotes each patient’s infection status. HBsAg is an HBV surface protein that can be detected in high quantities in serum during acute or chronic infection. The body can produce antibodies against HBsAg (anti-HBs), and the presence of anti-HBs indicates recovery from infection or immunity. The presence of anti-HBc denotes a previous or ongoing infection, while that of the hepatitis B core antigen (HBcAg) or its extracellular form HBeAg indicates active viral replication. On the other hand, antibodies against HBeAg (anti-HBe) indicate a decline in viral replication. Finally, the presence of IgM anti-HBc indicates acute infection (in past <6 months) while its absence indicates chronic infection (165).

Baseline liver dysfunction was observed among 17.2% of HBsAg-positive IBD patients. Among patients who have received immunosuppressants, the rate of liver dysfunction was higher among HBsAg-positive patients than among HBsAg-negative ones (166). HBV reactivation in IBD patients treated with IFX is described in several patients in Table 4 (167-174).

In a systematic review analyzing patients treated with anti-TNF agents with positive HBV markers, chronic HBV infection was classified as positive by the presence of HBsAg and resolved HBV infection was classified as positive by the presence of anti-HBc and/or anti-HBs antibodies (172). Both a diagnosis of IBD and treatment with IFX were risk factors for raised baseline liver transaminases among chronic HBV patients, as well as symptomatic disease. Elevated baseline transaminases were a further risk factor for liver failure (p = 0.016). Among patients with HBV reactivation, elevated serum HBV DNA alone is reported in 23.1% of subjects, 30.8% of patients experienced elevated serum HBV DNA with slightly raised liver transaminases levels, and 46.1% had elevated serum HBV DNA with biochemical manifestations of liver disease (172).

Based on baseline data using serum samples collected prior to initiating anti-TNF treatment, patients could be either known HBV carriers (serology performed prior to initiating anti-TNF treatment), have an unknown HBV status (serology performed after HBV reactivation using archival serum samples collected prior to initiating anti-TNF treatment), or presumed negative (serology performed prior to initiating anti-TNF treatment) in case reports. Symptoms of HBV reactivation can include fever, malaise, fatigue, nausea, loss of appetite, weight loss, weakness, dyspepsia, and joint and/or abdominal pain (169, 171-173). Hepatic manifestations are the predominant symptoms,
including hepatitis or jaundice with elevated AST, ALT, alkaline phosphatase (ALP), γ-glutamyl transpeptidase and total bilirubin. New onset ascites, presenting as severe hepatitis with ballooning degeneration, hepatocyte necrosis and fibrosis on biopsy was detected in one case (170). Liver dysfunction, with moderate infiltration of chronic inflammatory cells and mild fibrosis in the portal area, occurred in another patient (168).

Four patients were known to be chronic HBV carriers. The first three patients all show positive serum HBsAg (167-169). HBeAg and anti-HBe antigen were also positive in the first of these patients, (167), and anti-HBe and anti-HBc were positive in the other two patients (168, 169). ALT and AST levels were normal and HBV DNA was undetectable at baseline in the patients in which these parameters were assessed (167, 168). Serology analysis is unavailable for the fourth, but chronic HBV was noted in his medical history (170).

HBV reactivation is described in four patients with unknown HBV status prior to initiating IFX treatment. Two of these patients were found to be HBV carriers based on markers of HBV infection in serum collected at previous visits (169, 171). Archival serum was not available in a third patient (172), while results are not described in the fourth (173). In the two patients for whom archival serum was available, positive HBsAg and HBV DNA was determined in both (169, 171), while HBeAg and IgG anti-HBc antibodies were further found in one (169). A fifth patient with a previously unknown HBV carrier state was presumed negative at baseline, owing to negative serum HBsAg and liver transaminases within normal limits. Anti-HBc and anti-HBe antibodies were not assessed (174).

HBV reactivation, diagnosed as chronic cirrhotic hepatitis (AST 127 IU/L, ALT 122 IU/L and HBV DNA 3.9 × 10^8 copies/mL), occurred in a CD patient. Introduction of lamivudine prior to IFX exposure led to continuous AST and ALT normalization, yet high viremia persisted. The patient remained asymptomatic, with continued viral replication upon IFX introduction (175). No HBV reactivation was reported upon IFX exposure in another patient with a history of HBV infection (mildly elevated AST and ALT, and positive HBsAg, IgG anti-HBc, HBeAg and HBV DNA). Lamivudine was used to treat the initial HBV infection, resulting in resolution of symptoms, and was further maintained during IFX treatment (169).

The rate of HBV reactivation was 5.4% among patients with resolved HBV infection treated with anti-TNF agents in a systematic review. Among these 9 patients, symptoms of liver disease occurred in 2, with one death due to fulminant liver failure (172). No HBV reactivation was detected in two small sample of RA patients with resolved HBV infection treated with anti-TNF agents (176, 177). In general, anti-HBs titers decrease while on anti-TNF agents in patients vaccinated against HBV. Liver decompensation or significant increases in ALT levels were absent in patients with chronic HBV infection receiving anti-TNF agents. Viral reactivation while receiving lamivudine was observed in a patient with a mutant HBV strain (177).

The rate of HBV vaccination in a small sample of pediatric IBD patients was 87.0%. Among these, HBV immunity was achieved in 56.3% (serum anti-HBs level ≥10 mIU/mL). A booster vaccination led to immunity in 76.5% of patients who did not achieve initial immunity. No patient was classified as exposed to or chronic carrier of HBV (negative HBsAg or anti-HBc). Older age (p=0.001), lower albumin levels (p=0.01) and the presence of pancolitis (p=0.029) were risk factors for not developing protective antibodies. The dose, frequency and duration of IFX treatment, or concomitant exposure to immunomodulators, did not affect the rate of developing HBV immunity following vaccination (178).

**Hepatitis C Virus Infection**

TNF-α plays a key role in the host defense against HCV infection. However, high levels of TNF-α suppress IFN and its antiviral activity in HCV-infected patients (179-184). Anti-TNF-α agents were found to stabilize hepatitis, or even improve liver transaminases levels and HCV viremia in a review of 153 HCV patients treated with for RA, CD and other chronic inflammatory diseases (185). Liver functions remain unchanged in CD patient co-infected with HCV during treatment with IFX (186-188).

In a separate study, an HCV carrier patient treated with ADM for IBD experienced stable yet consistently detectable viremia with normal liver function test results (189), while 2 IFX patients developed biochemical changes in a retrospective
cohort of 4 IBD patients co-infected with HCV (190). Worsening of hepatic biochemical tests was observed in an UC patient with HCV and HIV co-infection undergoing anti-TNF treatment with concomitant 6-mercaptopurine. Deteriorating hepatic biochemical tests were attributed to progressive liver disease associated with HIV, and liver function improved upon reducing the dose of 6-mercaptopurine (191). Asymptomatic elevations of serum transaminases and progression of viremia was observed after the 14th IFX infection in an RA patient co-infected with HCV. The patient was also receiving methotrexate (192). Based on these findings, anti-TNF-α agents are generally considered safe in patients with chronic hepatitis, yet careful monitoring of liver function and viremia is strongly encouraged. A recent report demonstrated that the use of a single dose of TNF-α inhibitor was safe and well tolerated in HCV-infected study participants, corroborating the current body of evidence (193).

**Human Immunodeficiency Virus**

Treatment with IFX did not affect the CD4+ cell count and the viral load in a CD patient co-infected with HIV (194). CD4+ cell counts and viral loads were also unaffected by anti-TNF treatment in small RA samples co-infected with HIV (195, 196). IFX led to a quick increase in the CD4+ cell count in another patient. Long-term effects are unknown as the patient was lost to follow-up (197). In another CD patient co-infected with HIV and not receiving antiretroviral treatment, IFX decreased the CD4+ cell count through a mechanism believed to involve cell cycle inhibition and IL-10 mediated T cell apoptosis. The viral load also decreased in this patient (198).

No increase in the risk of infection is reported in an RA patient co-infected with HIV and treated intermittently with IFX over a 10 year period. The patient’s viral load remained undetectable or low while on antiretroviral medication, with CD4+ cell counts within reference range (199). Based on these findings, anti-TNF treatment is expected to have minimal effect on HIV viral load as well as on the CD4+ cell counts. Furthermore, IFX and ADM appear safe with regards to the risk of opportunistic infection in patients with higher CD4+ cell counts, especially those undergoing antiretroviral treatment (200).

**Cytomegalovirus**

CMV, also known as human herpes virus (HHV)-5, belongs to the herpesvirus family. CMV serology was positive in 70.0% of samples collected before IFX infusions in consecutive CD patients, indicating latent viral presence. CMV replication and reactivation was not observed (201). CMV was not detected in a pediatric IBD sample treated with biologicals or conventional therapies for over 12 months (202).

The role of CMV in IBD patients undergoing IFX treatment is unclear. On the one hand, the immunosuppressive conditions created by IFX are thought to lead to the reactivation of latent CMV infections, triggering inflammation and leading to exacerbations of colitis. As such, a dilemma exists with respect to treating IBD patients with CMV reactivation, as reducing immunosuppressive treatment can lead to worsening of IBD symptoms, while increasing immunosuppressive treatment to control IBD symptoms can lead to further CMV reactivation. Furthermore, the antigen or genetic detection of CMV in blood may not reflect CMV reactivation in the inflamed mucosa (203). However, detection of CMV in mucosal tissue is of value, particularly in patients with refractory UC. CMV reactivation was only detected in inflamed colonic mucosa. The use of antiviral therapy facilitated disease remission in 83.3% of treated patients. At the same time, patients negative for CMV reactivation benefited from an increase in the dose of immunosuppressive treatment, showing the benefits of early CMV detection in mucosa in patients with refractory UC (204). This can be explained by findings that pro-inflammatory cytokines such as IFN-γ and TNF-α lead to CMV reactivation in inflamed colonic mucosa. As such, CMV infection may initially be restricted to the inflamed mucosa where latently infected monocytes and dendritic cells reside, while active replication may lead to systemic inflammation (205). IFX treatment may lead to CMV clearance in refractive UC patients. Nakase and Chiba (206) show that IFX treatment led to negative CMV DNA in colonic mucosa in three patients with positive CMV DNA prior to IFX treatment.

Cases of CMV reactivation in CD patients treated with IFX are described in Table 4 (207-210). Common symptoms include fever, chills, fatigue, nausea and vomiting (207-210). Exacerbation of gastrointestinal symptoms occurred in three patients
Severe hemorrhagic ileocolitis with esophageal and duodenal ulcers were accompanied by impaired cerebral function with difficulty concentrating, impaired hearing and rapidly deteriorating short-term memory in a patient. CMV inclusion bodies were shown on colonoscopy (207). Ileocolitis with persistent disseminated intravascular coagulation and gastrointestinal hemorrhage was observed in a patient also afflicted by splenomegaly. CMV inclusion bodies were noted on splenectomy (208). In a pediatric patient, colitis with bloody diarrhea and thickening of the colon was accompanied by icteric sclera, respiratory distress and bilateral pulmonary infiltrates. CMV inclusion bodies were noted on colonoscopy. The patient subsequently died of multiorgan failure, including respiratory and subsequently hepatic failure (209). Hepatitis with AST 468 U/L, ALT 282 U/L, ALP 845 U/L and total bilirubin 1.1 mg/dL, as well as hepatomegaly without abnormalities of the biliary tract, was diagnosed in the fourth patient. CMV inclusion bodies were identified on liver biopsy (210).

Varicella Zoster Virus
VZV, also known as HHV-3, is associated with chickenpox in the pediatric population and with herpes zoster or shingles in adults. Chickenpox refers to primary VZV infection, characterized by low fever, nausea, malaise, headache and muscle aches, as well as vesicular, itchy rash affecting primarily the trunk and the head. Under conditions of immunosuppression, herpes zoster or shingles may occur as a result of latent VZV reactivation. This presents with blistering skin rash, typically on a more limited area of the body. The more limited presentation during VZV reactivation is due to the fact that only a few nerve cells produce the virus, hence cutaneous manifestations are limited to the area associated with the axons of those cells. The immune system prevents a more wide-spread activity. Multi-dermatomal distribution characterizes disseminated VZV (211).

VZV infection in IBD patients treated with IFX is described in several patients in Table 4 (212-220). The risk of herpes zoster was assessed in anti-TNF patients in the French research axed on tolerance of biotherapies registry. Herpes zoster occurred after a median 11.5 years of anti-TNF treatment. Herpes zoster occurred in patients treated with all of IFX and ADM, with 14.7% incidence for ADM and 37.5% incidence for IFX. Among anti-TNF agents, monoclonal antibodies were risk factors for VZV infections (220).

Primary VZV infection is believed to have occurred in two CD patients treated with IFX (212, 213). The first of these patients experienced fever, chills, nausea, vomiting and abdominal pain, as well as non-pruritic pustules on chest and back, resembling pustular folliculitis. In addition, elevated AST (210 IU/L) and ALT (227 IU/L), and normal ALP and bilirubin were also found. Along with hepatomegaly, this shows evidence of hemorrhage and necrosis surrounding the central veins. Fulminant hepatic failure and respiratory failure occurred. Despite the severe disease course, this was diagnosed as a primary infection due to a lack of IgG or IgM on varicella serology (212). In another case, multiple fluid-filled vesicular lesions spread over the entire body are described in a child. These were accompanied by mild pharyngitis without fever or associated systemic symptoms (213).

Herpes zoster is described in several cases comprising both pediatric and adult patients (213-218). IFX [incidence rate (IR) 2.4 per 1000 patient-years, 95% CI 0.0-4.7] and ADM (IR 7.1 per 1000 patient-years, 95% CI 2.9-11.3) were associated with herpes zoster in a large Belgian cohort of patients treated with biologicals (216). Herpes zoster occurred at the site of IFX infusion in a CD patient with a history of childhood varicella, manifesting as erythematous pruritic papulovesicles. The reaction reoccurred upon subsequent infusions. Eventually, valacyclovir prophylaxis prevented viral reactivation (215). Painful swelling associated with an erythematous, purpuric rash occurred after the resolution of an initial vesicular rash in a young patient. It is unknown whether this is a primary VZV infection, but a diagnosis of herpes zoster was made based on the localization of the rash in the suprascapular and subclavicular regions. A further relapse of lesions was reported at a later date (214). Disseminated cutaneous zoster infection, manifesting as pruritic, nonpainful, vesicular lesions involving the scalp, face, trunk and extremities, with no systemic symptoms, is described in a child one year after a primary VZV infection and subsequent VZV immunization (213).

Four cases of herpes zoster with dermatomal distribution are further described. These can be further accompanied by fever, nausea, headache and
pain (216, 218). A papular rash along the thoracic dermatome characteristic of herpes zoster occurred in a CD patient treated with IFX who developed a severe CMV infection (207). A case of VZV reactivation manifesting as vesicular maculopapular rash with dermatomal distribution was accompanied by meningitis with increasing headaches and photophobia in a CD patient treated with ADM. Leukocytosis and elevated protein levels in CSF were also found (217).

Seven additional non-serious VZV cases, likely reflecting opportunistic infections, are reported in two cohorts of CD patients treated with IFX (219, 220). VZV reactivation is reported in another CD patient treated with ADM (221).

**Herpes Simplex Virus**

HSV-1 and -2, also known as HHV-1 and -2, can cause blisters on the skin or on the mucous membranes of the mouth, lips or genitals. A case of localized oral HSV infection is reported in a CD patient treated with ADM in a cohort study. The patient was successfully treated with acyclovir (221). Non-serious HSV infection manifesting as genital herpes is reported in a 49 year old female CD patient treated with IFX (219). Valaciclovir prophylaxis successfully prevented HSV-1 reactivation in a CD patient with a history of HSV-1 infection (222).

**Epstein-Barr Virus**

EBV, also known as HHV-4, is another member of the herpesvirus family. EBV positivity is an important infectious adverse event as it can lead to both malignant and non-malignant complications (223). EBV serology was positive in 98.3% of serological samples collected before IFX infusions in consecutive CD patients, showing latent viral presence (201). However, EBV replication and reactivation was only observed in 11.7% of patients at week 0, 3.3% at week 2, and 3.3% at week 14, with low viremia (50-600 copies/mL), indicating transient replication. Concomitant methotrexate was associated with EBV viremia by polymerase chain reaction (PCR) (OR 7.5, 95% CI 1.4-40.1, p=0.025) (201).

Risk factors for detectable EBV DNA in whole blood include IBD, regardless of treatment, compared to healthy volunteers (p<0.05), IFX compared to non-biological treatments, age ≥60, and UC compared to CD (223). A 17 year-old IBD patient whose blood tested positive for EBV was treated with IFX without any reported adverse events (202). Non-serious EBV infection manifesting as mononucleosis is reported in a 15 year old female CD patient treated with IFX and 6-MP (219).

**Other Members of the Herpes virus Family**

The remaining members of the herpesvirus family are HHV-6, HHV-7 and HHV-8. No patient became positive for HHV-6, HHV-7 and HHV-8 in blood samples at any point in a sample of 60 consecutive CD patients treated with IFX (201). HHV-6 was not detected in urine, serum or peripheral blood mononucleated cells in a pediatric IBD cohort treated with biologicals or conventional therapies for over 12 months (202).

However, several findings support the monitoring of HHV-6 levels in patients treated with biologicals. Recently, Al Jawhari et al. (224) reported that 20 of 55 (36.4%) colon biopsies belonging to patients with gastrointestinal conditions tested positive for HHV-6 by qualitative PCR, showing that HHV-6 is present in the intestinal tract. HHV-6 was associated with diarrhea (224). Elsewhere, HHV-6 was found to induce the replication of JCV in a limited number of NTZ patients (225).

**John Cunningham Virus**

Progressive multifocal leukoencephalopathy (PML) is a rare but often fatal opportunistic infection caused by John Cunningham virus (JCV) reactivation in immunosuppressed patients (226). The presence of JCV was determined by PCR amplification in several matrices, including serum, urine, peripheral mononuclear blood cells and intestinal biopsies in CD patients with immune-mediated diseases treated with IFX or non-biological agents, and in healthy controls (202, 226, 227). JCV was quantified by PCR in 37.0% of patients treated with IFX and in 17.0% of patients treated with non-biological agents in pooled data collected at four time points over 1 year of treatment. Differences between the two cohorts were significant with respect to JCV positivity in urine (p=0.03), plasma (p<0.05) and colorectal biopsies (p=0.02) (226). JCV DNA was detected more frequently in urine than in either serum or peripheral mononuclear blood cells (202, 227). Viremia in urine was significantly higher in IFX
patients compared to patients treated with non-biological agents at one year of follow up only (7.47 vs. 5.36 log genome equivalents/mL, p=0.039) (226). Finally, odds of detecting JCV in urine were higher in IBD patients than in healthy controls (p<0.05) (202, 227). The prevalence of transiently-positive JCV in peripheral mononuclear blood cells measured by PCR was also higher in IBD patients, yet the viral load was low and comparable between groups (227). These studies show that while IFX is associated with modest JCV reactivation in peripheral mononuclear blood cells, this did not reach levels associated with PML (227).

**Influenza**
The rate of developing immunity to influenza following vaccination was lower in a pediatric IBD sample receiving immunomodulatory treatment, either alone or in combination with IFX, compared to healthy controls (228). Compromised immune responses to the influenza vaccine are thought to involve impaired effector and memory B cell and antibody response. The compromised antigen responsiveness may also account for more severe influenza manifestations among individuals receiving immunomodulatory treatment compared to healthy controls (229). In a separate study, the rate of developing immunity to influenza (antibody titer ≥1:40) was high and comparable between anti-TNF patients, patients treated with other immunomodulators, and healthy controls. However, antibody titers were significantly lower in anti-TNF patients compared to the other two groups (230). Acute hepatic cytolysis is reported in response to H1N1 vaccination in a CD patient following one IFX infusion. ALT and ASD were elevated 2-3 times over the upper limit of normal during this time, with spontaneous resolution (231).

**INFECTIOUS ADVERSE EVENTS WITH INTEGRIN ANTAGONISTS**
PML is the most worrisome adverse event of NTZ. The risk of PML in NTZ patients was investigated in patients treated with NTZ for RA, multiple sclerosis or CD (232). Patients previously involved in clinical trials with NTZ underwent clinical history, physical exam, magnetic resonance imaging of the brain, and CSF analysis for JCV DNA. From 3826 recruited individuals, 3 patients were diagnosed with PML. One patient survived and 2 patients died. The study concluded that the risk of PML in patients treated with this integrin antagonist for a mean period of 17.9 months was 1 in 1000 patients. Due to the risk of PML, NTZ was voluntarily withdrawn from the market in 2005 (232). Subsequently, NTZ was used for the treatment of multiple sclerosis in the TOUCH prescribing program, under a strict post-marketing surveillance program that incorporates mandatory education, monitoring, and reporting to the FDA (233). Currently, NTZ is available, and it can be prescribed in moderate to severe CD patients who have failed standard and anti-TNF therapies, and who have biologic evidence of inflammation. A positive anti-JCV antibody status is considered to be a risk factor for PML development, particularly with prolonged NTZ use (234). Testing for JCV should be used to stratify individual patients’ risk for PML prior to NTZ introduction (235).

One case of fatal PML associated with JCV is reported in a patient treated with NTZ for active CD in the ENACT-2 trial (236). In the ENCORE trial, one patient treated with NTZ developed a serious infection (perianal abscess) that was not considered to be related to NTZ use. No cases of PLM were reported in this study (237). No patient developed PML in two small samples of CD patients treated with NTZ (238, 239). Of 5 patients tested in one study, 4 (80.0%) were positive for anti-JCV antibody (238). Six (54.5%) of 11 patients tested in the other study were positive for anti-JCV antibody (239). One patient in each study discontinued treatment as a result of the positive test (238, 239).

VDZ binds the α4β7 integrin and is therefore used as anti-adhesion molecule therapy in IBD. Latent TB, as well as one case each of lethal culture-negative sepsis and septic-shock, were reported in CD patients treated with VDZ in the GEMINI 2 trial. There were no cases of PLM in this study (240). In contrast, no serious infections, including PML, were noted in UC patients in the GEMINI 1 trial (241). Infections were the most common adverse events in the GEMINI 3 trial, in which active CD patients who previously failed other treatments were treated with either VDZ or placebo. Two cases of serious infections were noted in VDZ patients (anal abscess and urinary tract infection), neither of which led to treatment interruption (242).

The expression of the αEβ7 integrin is elevated in active UC and CD (243). There is an interaction between the αEβ7 integrin and E-cadherin that
guides T cells to the intestinal mucosa and promotes the binding to their ligands, mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) and E-cadherin. MAdCAM-1 expression is increased in patients with UC and CD. ETZ is a humanized IgG1 monoclonal antibody which targets the β7 subunit of both the α4β7 and αEβ7 integrins. ETZ blocks the binding of αEβ7 to its ligand E-cadherin. Thus, ETZ could affect leukocyte composition within the intestinal mucosa by blocking α4β7-expressing leukocytes from entering the intestinal mucosa and inhibiting their extravasation through MAdCAM-1-expressing mucosal endothelial venules. Therefore, ETZ inhibits leukocyte homing to the mucosa and avoid the withholding of leukocytes in the intraepithelial space of the intestinal mucosa (244).

A phase II double-blind, randomized, placebo-controlled trial of ETZ in patients with moderate to severe UC showed its efficacy in achieving clinical remission after 10 weeks of therapy (245). In this trial, patients who were non responders to anti-TNF therapy were assigned to receive one of two doses of subcutaneous ETZ or placebo. Clinical response and remission in patients treated with ETZ at either the lower dose (100 mg) or the higher dose (300 mg) were significant higher compared to patients receiving placebo after 10 weeks of therapy. Furthermore, biomarker analysis revealed that in treated patients, β7 receptors were fully occupied in the peripheral blood and in the colonic tissue. No serious opportunistic infections were reported (245). Furthermore, no PML was observed in a small sample of moderate to severe UC patients treated with ETZ elsewhere (246). A phase III, double blind, placebo-controlled, multicenter study is ongoing, investigating the efficacy and safety of ETZ for the induction and maintenance of remission in patients with moderately to severely active UC who are refractory to or intolerant of TNF inhibitors (http://www.clinicaltrials.gov/ct2/show/NCT02100696?term=ruMAb+Beta7&rank=9).

Approximately 1.4 million persons in the US and 2.2 million persons in Europe have IBD. Variation in presentation and disease course suggests that environmental factors significantly modify the development of CD and UC, which further excludes the homogene therapy in IBD and vote for personalized approach. Moreover, multiple factors may influence the pharmacokinetics of anti-TNF agents and integrin antagonists, such as antigen load, albumin, immunogenicity, concomitant immunosuppressive use, immunocompetent or immunosuppressed status of the individual patient, as well as previous infections. In their 2012 review on TNF antagonist, Ordás et al. suggested the need of therapeutic monitoring of these agents in order to allow rational dose selection and treatment optimization in individual patients during both the induction and maintenance phases of treatment, resulting in greater efficacy (247).

**CONCLUSION**

Biological therapies are target-specific and often more efficacious than the traditional immunosuppressive therapeutics used in IBD. IBD is a lifelong, chronic disorder associated with significant morbidity. While anti-TNFαt agents have dramatically improved the symptoms and long-term outcomes for many patients with UC and Crohn’s disease. However, side effects are common and rates of primary and secondary nonresponse are high. As such pharmacologic agents aimed at other targets are much needed for patients with moderate-to-severe disease. The aim of this review was to present an integrative approach that bridges preclinical and clinical research looking at different aspects of monitoring biological therapies in clinical and laboratory settings. De novo infections and reactivation of latent infectious agents are complex processes, and represent an increasingly relevant clinical health problem. With the use of biological therapies in IBD, a disease in which the microbiome is involved, reactivation of latent bacterial and viral infections may occur, and this can change the immune and biological balance interplaying with internal and external triggers. In particular, there is increasing awareness regarding latent virus reactivation. This occurs when a latent virus is reactivated into its active replicative phase as a result of an internal or external trigger, such as immunosuppression.

However, to attribute the risk of viral reactivation to biological therapy alone is not plausible because the underlying malignant or autoimmune condition could also be a contributing factor. This is also the case considering viral reactivation to biological therapy in RA and psoriatic arthritis. There is well documented evidence regarding the reactivation of viruses such
as HBV, HHV-6 and CMV with non-biological drugs. Long-term data are lacking; such data are essential to guide risk stratification and chemoprophylaxis. Universally accepted viral screening guidelines prior to use of immunosuppression are lacking. As an example, HBV screening prior to commencing immunosuppression, but this action has not translated into universally accepted guidelines. Some of the other relevant viruses involved include CMV and HCV. Providers and specialty resources are required including gastroenterology, radiology, surgery, pharmacy and laboratory services. We suggest that the clinician should work with the laboratory specialists for a successful therapeutic intervention. Screening procedures for relevant viral and bacterial infections are necessary prior to beginning biological therapy. Moreover, continuously monitoring the levels of TNF-α in patients undergoing anti-TNF therapies, as well as the levels of integrins and cadherin in patients undergoing anti-integrin therapies, will ensure a balance of immune reaction in the clinical setting even prior to starting immunosuppression in IBD. These continuously evolving areas of science, medicine and biopharmaceuticals are becoming increasingly important for clinicians. The focus should be on molecular mechanisms of biological therapies directed towards IBD and how the use of the therapies impacts the immune system. We strongly encourage the collaborations of health professionals with different interests in clinical efficacy, therapeutic drug monitoring and clinical toxicology. The main concern should be pharmacovigilance. Therefore, monitoring biomarkers and infectious diseases should be the aim not only in clinical trials but also in daily practice. Long-term outcomes of latent viral reactivation with different classes of biological therapy are essential to help clinical decisions and patient counseling, with informed consent of the individual regarding possible latent viral reactivation and bacterial infections being part of it. This strategy would allow a personalized approach to therapy that should be more effective and safer. Therapeutic monitoring in patients with IBD under TNF and integrin antagonist treatment has the potential for improving patient safety and important cost utility of therapy.

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Table 1. TB in anti-TNF-treated IBD Patients

| Ref | Patients Demographics | Drug | Co-medication/co-infections | Type Infection; Method of Detection | Outcome |
|-----|-----------------------|------|-----------------------------|------------------------------------|---------|
| 70  | 53 M - CD Spain Screening not performed | IFX (2 infusions) | Steroid dependent | *M. tuberculosis* Culture | Anti-TB treatment Resolution of symptoms |
| 71  | 24 M - CD Netherlands Normal chest X-ray | IFX (4 doses over 10 months) | Prednisone | *De novo M. tuberculosis* infection Culture | Isoniazid, rifampin and ethambutol, pyrazinamide Paradoxical reaction Partially recovered after 1 year |
| 72  | 28 M - CD Scotland Normal chest X-ray | IFX for 2 months | Azathioprine | Pulmonary TB Acid, alcohol fast bacilli Culture | Standard quadruple anti-TB chemotherapy Immune reconstitution inflammatory syndrome Resolution of symptoms Tuberculostatic drugs Eventual recovery following bacterial pulmonary abscess and herpetic stomatitis |
| 73  | 47 M from Pakistan Indeterminate colitis Spain TST negative Normal chest X-ray | IFX (3 infusions) | Azathioprine HIV with normal CD4+ T cell counts 368/mm² and viral load 3600/mL efavirenz and tenofovir | Pulmonary and thoracic TB Lymph node fine-needle puncture | Tuberculoid granulomas in liver and spleen Culture Quadruple TB therapy Paradoxical reaction Resolution of symptoms |
| 74  | 68 F IBD France TST negative Normal chest X-ray | ADM for 2 months | Long-term glucocorticoids Untreated primary TB, initially unreported | Tuberculoid granulomas in liver and spleen Culture | Quadeiple TB therapy Paradoxical reaction Resolution of symptoms |
| 75  | 52 M - CD USA QFT-G and TST positive; Normal chest X-ray | IFX for 4 months ADM for 1 month | Isoniazid, pyridoxine treatment; prophylaxis 11 months; Prednisone | Pulmonary TB with liver and spleen lesions; Culture | Isoniazid, rifampin, ethambutol and pyrazinamide Resolution of symptoms |
| 76  | 38 M - CD Korea TST positive Normal chest X-ray | IFX (3 infusions) | Methylprednisolone | Miliary TB; nodular spleen lesions; TST positive; Acid fast bacilli Culture, Genetic detection | Isoniazid, rifampin, pyrazinamide and ethambutol Paradoxical reaction Resolution of symptoms |
| 77  | 53 F - CD Serbia TST negative Normal chest X-ray | IFX (3 infusions over 3 months) | Azathioprine | Miliary TB Culture | Isoniasid, rifampicin, streptomycine, pyrazinamide and ethambutol Resolution of symptoms |

Continue………………..
| Ref | Patients Demographics | Drug | Co-medication/ co-infections | Type Infection; Method of Detection | Outcome |
|-----|-----------------------|------|-------------------------------|-----------------------------------|---------|
| 78  | 4 M CD                | IFX for 16 months | Corticosteroids Azathioprine | Cerebral tuberculomas, lung, mediastinal and abdominal nodes, skin involvement Genetic detection, culture | Anti-TB treatment Resolution of symptoms |
|     | West Europe           |      |                               |                                   |         |
|     | TST negative          |      |                               |                                   |         |
|     | Normal chest X-ray    |      |                               |                                   |         |
|     |                      |      |                               |                                   |         |
| 80  | 64 M- CD              | IFX (7 infusions over 5 months) | Azathioprine | Peritoneal TB QFT-G Genetic detection Culture | Isoniazid, rifampicin, pyrazinamide and ethambutol Improvement of patient condition |
|     | Germany               |      |                               |                                   |         |
|     | TST negative          |      |                               |                                   |         |
| 81  | 21 M- CD              | IFX | Not specified | Anal TB Acid-fast bacilli Culture | Isoniazid, rifampin and pyrazinamide Paradoxical reaction Recovered after 9 months of non-steroidal anti-inflammatory drugs |
|     | Spain                 |      |                               |                                   |         |
|     | TST unknown           |      |                               |                                   |         |
|     | Normal chest X-ray    |      |                               |                                   |         |

ADM: adalimumab; CD: Crohn's disease; F: female; IFX: infliximab; M: male; QFT-G - QuantiFERON-TB Gold test; TB: tuberculosis; UC: ulcerative colitis
### Table 2. Bacterial Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection and Method of Detection | Outcome |
|-----|-----------------------|------|------------------------------|------------------------------------------|---------|
| 85  | 60 M                  | IFX for 6 months | n/a                         | *M. marinum* Culture                      | Minocycline Resolution of symptoms |
|     | Crohn’s ileocolitis   |      |                              |                                          |         |
|     | USA                   |      |                              |                                          |         |
| 85  | 33 F                  | IFX (2 infusions) | n/a                         | *M. marinum* Acid fast bacilli, Culture  | Rifampin and doxycycline Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 86  | 50 M                  | IFX (4 infusions) | Oral immuno-suppressants    | Cutaneous *M. marinum* infection Culture | Minocycline, ethambutol and clarithromycin Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 87  | 40 M                  | ADM for 3 months | n/a                         | *M. marinum* Acid fast bacilli Culture; TST positive IFN-γ release positive | Rifampicin and ethambutol Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 88  | 37 F                  | IFX over 2 years | Azathioprine, mesalazine    | *M. marinum* Culture Genetic detection  | Minocycline, doxycycline and clarithromycin Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 89  | 63 M                  | IFX over 3 years | n/a                         | *M. marinum* Culture                      | Minocycline Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 90  | 32 M                  | IFX for 6 weeks | Prednisone, mesalazine and metronidazole | *M. marinum* Acid fast bacilli Culture | Ethambutol and rifampicin Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 91  | 36 F                  | IFX for 2 years | Anti-depression medication  | *M. avium* complex Acid fast bacilli Culture | Rifampin, ethambutol, ciprofloxacin and azithromycin Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 92  | 11 F                  | IFX for 4 months | Mesalazine, corticosteroids and 6-mercaptopurine | *M. avium complex QFT-G positive Culture | Ethambutol, clarithromycin and rifampin Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 94  | 67 M                  | IFX (3 infusions) | Prednisone, azathioprine, mesalazine | *L. monocytogenes Blood culture | Amoxicillin and clavulanic acid Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 95  | 48 M                  | IFX (1 infusion) | n/a                         | *L. monocytogenes Blood culture | Ampicillin, gentamycin and metronidazole Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
| 96  | 68 M                  | IFX (2 infusions) | Prednisone and azathioprine | *L. monocytogenes Blood culture | Amoxicillin and clavulanic acid Resolution of symptoms |
|     | CD                    |      |                              |                                          |         |
Table 2 (Continued). Bacterial Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/ co-infections | Type of Infection and Method of Detection | Outcome |
|-----|----------------------|------|------------------------------|------------------------------------------|---------|
| 97  | 37 M- CD Canada      | IFX (2 infusions) | Azathioprine and corticosteroids | *L. monocytogenes* CSF and blood culture | Ampicillin, gentamicin and trimethoprim-sulfamethoxazole, Resolution of symptoms |
| 98  | 50 F- CD Spain       | IFX (3 infusions) | Azathioprine                  | *L. monocytogenes* Blood and CSF culture | Ampicillin and gentamicin, Resolution of symptoms |
| 99  | 17 F- CD USA         | IFX (1 infusion) | 6-mercaptopurine, mesalazine, prednisone, methylprednisolone | *L. monocytogenes* Blood culture | Ampicillin and trimethoprim-sulfamethoxazole, Resolution of symptoms |
| 100 | 34 M- CD France      | IFX (3 infusions) | Mesalazine, azathioprine      | *L. monocytogenes* Blood culture, Meningitis | Ampicillin and gentamicin, Resolution of symptoms |
| 101 | 19 M- CD Spain       | ADM over 3 months | Azathioprine                  | *L. monocytogenes* Blood culture, Meningitis | Ampicillin and gentamicin, Partial resolution of symptoms |
| 102 | 17 M- UC USA         | IFX (1 infusion) | Mesalazine, prednisone        | *L. monocytogenes* CSF and blood culture | Meropenem, gentamicin, Resolution of symptoms |
| 103 | 51 F- UC Portugal    | IFX (2 infusions over 5 weeks) | Steroids | *L. monocytogenes* Blood culture | Ampicillin, Resolution of symptoms |
| 104 | 64 F- CD Canada      | IFX (1 infusion) | Prednisone, mercaptopurine, glyburide | *L. monocytogenes* Blood culture | Treatment not specified, Resolution of symptoms |
| 39  | 39 F- CD Sweden      | IFX (3 infusions) | Prednisolone, mercaptopurine, mesalazine | *L. monocytogenes* Blood culture | Treatment not specified, Partial resolution of symptoms |
| 20  | 20 M- CD Italy       | IFX (1 infusion) | Methylprednisolone, azathioprine, mesalazine, metronidazole | *L. monocytogenes* Meningitis | Treatment not specified, Death |

Continue……………….
Table 2 (Continued). Bacterial Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/ co-infections | Type of Infection and Method of Detection | Outcome |
|-----|----------------------|------|-----------------------------|------------------------------------------|---------|
| 105 | 35 F- CD Spain       | IFX (2 infusions) | Azathioprine | L. monocytogenes CSF culture Meningitis | Ampicillin and gentamycin Resolution of symptoms |
| 106 | 50 F- CD Hungary     | IFX (episodic)   | Methyl-prednisolone | L. monocytogenes CSF culture Meningitis | Ampicillin and amikacin Resolution of symptoms |
| 111 | 27 F- CD France      | IFX (1 infusion) | Azathioprine and prednisone | L. pneumophila Urine antigen detection Culture | Rifampicin Resolution of symptoms |
| 112 | 71 M- UC Italy       | IFX (1 infusion) | Mesalazine | L. pneumophila serotype 1 Genetic detection | Antibiotics Death due to septic shock |
| 113 | 58 M- CD Germany     | IFX (3 infusions) | Azathioprine | L. pneumophila serotype 1 Urine antigen detection Genetic detection | Piperacillin-tazobactam and moxifloxacin Resolution of symptoms |
| 114 | 26 M- CD Canada      | IFX (1 infusion) | Morphine 6-mercaptopurine Smoking history | L. pneumophila serotype 1 Urine antigen detection | Piperacillin-tazobactam, vancomycin, azithromycin, caspofungin, followed by azithromycin Partial resolution of symptoms |
| 115 | 26 F- CD Netherlands | IFX (10 infusions over 17 months) | n/a | L. pneumophila serotype 1 Urine and serum antigen detection | Erythromycin Resolution of symptoms |
| 116 | 40 F- CD Germany     | IFX (6 infusions) | Mesalazine | S. aureus Culture | Moxifloxacin, imipenem, vancomycin and clarithromycin Death due to respiratory failure |

Continue……………….
| Ref | Patient Demographics | Drug | Co-medication/ co-infections | Type of Infection and Method of Detection | Outcome |
|-----|----------------------|------|------------------------------|------------------------------------------|---------|
| 118 | 29 M- CD USA          | IFX  | n/a                          | Methicillin-resistant *S. aureus*; Culture Acid fast bacilli; CT-guided needle aspirate | Vancomycin, rifampin and trimethoprim-sulfamethoxazole Four-drug anti-TB treatment Resolution of symptoms |
| 119 | 63 F- UC Portugal     | IFX (3 infusions) | Prednisolone | *S. aureus* Culture | Ciprofloxacin and vancomycin Resolution of symptoms |
| 120 | 32 Caucasian M- CD Japan | IFX over 2 years | Prednisolone | *S. aureus* Culture | Intravenous antibiotics Partial resolution of symptoms |
| 121 | 31 M- CD Japan        | IFX (9 infusions) | n/a                          | *E. coli*; Methicillin-resistant *S. aureus* Culture Screening agar *N. meningitidis* group C/W135; CSF antigen detection | Vancomycin, teicoplanin; Surgery, then teicoplanin, meropenem; Fluconazole for catheter-related *C. parapsilosis* Resolution of symptoms |
| 122 | 51 F- CD USA          | CZP for 6 months | n/a                          | *N. meningitidis* group C/W135; CSF antigen detection | Ceftriaxone Resolution of symptoms |
| 123 | 45 M- CD Canada       | IFX (5 infusions) | Budesonide, mesalazine, ciprofloxacin and metronidazole Genetic detection *Nocardia species* | *S. aureus and M. marinum* infection suspected | Cloxacillin, then minocycline, then trimethoprim-sulfamethoxazole Resolution of symptoms |
| 124 | 61 M- CD USA          | IFX over 1.5 years | n/a                          | *Nocardia species* Skin biopsy | Trimethoprin-sulfamethoxazole Resolution of symptoms |
| 125 | 53F CD Spain          | IFX (3 infusions) | Prednisone, azathioprine | *N. cyriacigeorgica* Culture | Levofoxacin, meropenem, trimethoprin-sulfamethoxazole, amikacin, imipenem Resolution of symptoms |
| 126 | 81 M- CD USA          | IFX over 6 months | Mesalazine, 6-mercaptopurine | *N. pneumonia* Culture | Trimethoprin-sulfamethoxazole Resolution of symptoms |
| 127 | 20 M- UC Spain        | IFX  | Azathioprine, prednisone     | *P. aeruginosa* cavitary pneumonia | Treatment not specified Resolution of symptoms |

Continue ……………
## Table 2 (Continued). Bacterial Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection and Method of Detection | Outcome |
|-----|----------------------|------|-----------------------------|------------------------------------------|---------|
| 128 | 71 M- UC Scotland    | IFX (1 infusion) | Balsalazide, prednisolone, azathioprine | *P. aeruginosa* bronchopulmonary pneumonia Culture | Ischemic heart disease; mild chronic obstructive pulmonary disease; Inotropes and broad-spectrum antibiotics Death from septicemia |
| 129 | 68 M- CD USA         | IFX over 15 months | n/a | *S. enteritidis* Culture | Levofloxacin Resolution of symptoms |
| 130 | 35 M- CD Germany     | IFX (1 infusion) | Azathioprine | *S. typhimurium* Culture | Piperacillin-sulbactam, ciprofloxacin and metronidazole Resolution of symptoms |
| 131 | 67 M-UC France       | IFX over 1 month | n/a | *C. difficile* toxin Culture | Ofloxacin, then ciprofloxacin Resolution of symptoms |
| 132 | 31 M- CD Germany     | IFX | Azathioprine | *S. enterica* serovar Minnesota Culture | Meropenem and vancomycin, then ceftriaxone Resolution of symptoms |

ADM: adalimumab; CD: Crohn's disease; F: female; IFX: infliximab; M: male; UC: ulcerative colitis

## Table 3. Fungal Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of detection | Outcome |
|-----|----------------------|------|-----------------------------|------------------------------------------|---------|
| 137 | 51 M- CD Netherlands | IFX  | Azathioprine, then methotrexate | *P. jirovecii* pneumonia Staining in broncho-alveolar lavage | TR-SMX, prednisolone Resolution of symptoms |
| 138 | 29 M- CD France      | IFX (1 infusion) | Prednisolone, then azathioprine | *P. jirovecii* pneumonia Staining in broncho-alveolar lavage | TR-SMX, Resolution of symptoms |

Continue …………
| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of detection | Outcome |
|-----|----------------------|------|-----------------------------|---------------------------------------|---------|
| 139 | 19 M- CD USA         | IFX (14 infusions over 21 months) | Prednisone, then azathioprine       | *P. jiroveci* pneumonia Staining in bronchoalveolar lavage; Oral *Candida albicans*; Brushings of oral plaques | TR-SMX; No treatment for *C. albicans* co-infection Resolution of symptoms |
| 140 | 77 F- CD Greece      | IFX (6 infusions over 8 months)  | Methylprednisolone and azathioprine Glybenclamide for type II diabetes mellitus | *P. jiroveci* pneumonia Immunofluorescence Pulmonary *N. asteroides* Staining in bronchoalveolar lavage; Oropharyngeal infection with *C. albicans* Oral swab Airways infection with *A. baumanii*, Pulmonary *P. mirabilis*, Culture | TR-SMX for *P. jiroveci* Voriconazole for *C. albicans* Meropenem for *A. baumanii* and *P. mirabilis* Resolution of symptoms |
| 141 | 57 F- CD Japan       | IFX (4 infusions)                | Mesalazine, prednisolone azathioprine | *P. jiroveci* pneumonia Staining in bronchoalveolar lavage | TR-SMX and methylprednisolone, then pentamidine Recovered after surgery for the removal of a micro-abscess Levofloxacin, metronidazole and vancomycin, then TR-SMX and methylprednisolone Resolution of symptoms |
| 142 | 36 F- CD USA         | IFX (2 infusions)                | 6-mercaptopurine, mesalazine and prednisone | *P. jiroveci* pneumonia Staining in bronchoalveolar lavage | Imipenem, ciprofloxacin and metronidazole, then TR-SMX Resolution of symptoms |
| 143 | 45 M- UC Spain       | IFX (2 infusions)                | Azathioprine, prednisone and mesalazine | *P. jiroveci* pneumonia Staining in bronchoalveolar lavage | Continue ...... |
Table 3 (Continued). Fungal Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of detection | Outcome |
|-----|----------------------|------|------------------------------|----------------------------------------|---------|
| 144 | 36 M- CD Mexico      | ADM for 8 weeks | Azathioprine and prednisone Smoking history | *P. jirovecii* pneumonia Silver staining on bronchial lavage Direct immunofluorescence | Imipenem, clarithromycin, TR-SMX Resolution of symptoms Continue……………… |
| 145 | 56 F- CD USA         | IFX over 12 months | 6-mercaptopurine | Disseminated *Histoplasma capsulatum*; Serum antigen detection; Gomori’s methenamine silver staining on pathology | Itraconazole Surgery Resolution of symptoms |
| 146 | 8 M- CD USA          | IFX over 15 months | Mesalazine and 6-mercaptopurine Corticosteroids | *H. capsulatum* Urine antigen detection Culture *P. jirovecii* Silver staining on pathology specimens | Itraconazole, TR-SMX Partial resolution of symptoms |
| 147 | 16 F- Pediatric CD USA | ADM (4 doses) | 6-mercaptopurine | Systemic *Histoplasma sp.* histoplasmosis; Urine antigen detection; Complement fixation positive | Itraconazole Resolution of symptoms |
| 14  | 14 F- Pediatric CD USA | IFX (2 infusions) | Methotrexate | Histoplasmosis ; Urine antigen detection; Complement fixation positive | Amphotericin and intraconazole Resolution of symptoms |
| 13  | 13 M- Crohn’s colitis USA | IFX (7 infusions) | 6-mercaptopurine | Pulmonary histoplasmosis Urine antigen detection Complement fixation positive | Itraconazole Resolution of symptoms |
| 15  | 15 F- Pediatric CD USA | IFX (5 infusions) | 6-mercaptopurine | Pulmonary histoplasmosis with adenopathy Urine and serum antigen detection Complement fixation positive | Amphotericin and intraconazole Resolution of symptoms |

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Table 3 (Continued). Fungal Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug                           | Co-medication/co-infections | Type of Infection; Method of detection | Outcome                                      |
|-----|----------------------|--------------------------------|-----------------------------|----------------------------------------|----------------------------------------------|
| 147 | 21 M- Crohn’s colitis USA | IFX (13 infusions)           | 6-mercaptopurine            | *H. capsulatum*: Serum antigen detection; Complement fixation positive; Culture | Itraconazole Resolution of symptoms          |
| 148 | 40 M- CD USA          | IFX over 12 months            | Prednisone                  | *H. capsulatum*: Reactivation Culture  | Itraconazole Resolution of symptoms          |
| 149 | 43 M- CD USA          | IFX for 18 months             | Prednisone and azathioprine | *H. epiglottitis*: Biopsy, Culture, Serum antigen detection | Amphotericin and itraconazole Resolution of symptoms |
| 150 | 25 M- CD Netherlands  | IFX (1 infusion)              | n/a                         | *A. fumigatus*, Culture Serum antigen detection *Post-mortem* growth identified in lungs | Invasive aspergillosis Death Antibiotics and fungostatic therapy Death |
| 151 | 69 F- CD Switzerland  | ADM over 1 year               | Pre-existing renal insufficiency and chronic metabolic acidosis | Bronchoscopy | *Invasive aspergillosis* Death |
| 152 | 55 F- CD USA          | IFX (1 infusion)              | Azathioprine and methylprednisolone Interferon and ribavirin for HCV cirrhosis | Pulmonary infection with *C. species*, Culture *Aspergillus* sp. (post-mortem identified as *A. fumigatus*), Culture | Fluconazole initially for candidiasis Amphotericin B added for aspergillosis Death from multiorgan failure |
| 153 | 20 M- CD USA, Spain   | IFX over 3 months             | Prednisone 6-mercaptopurine  | *N. brasiliensis*; *A. fumigatus*; *A. niger*, Culture | Liezolid and voriconazole Patient lost to follow-up |
| 154 | 61 M- CD USA          | IFX over 2.5 years            | Prednisolone Severe hip osteonecrosis | Asymptomatic *C. neoformans*, Culture Immunohistochemistry | Amphotericin B and fluconazole Fluconazole substituted for amphotericin B due to renal insufficiency Resolution of symptoms Continue …….
Table 3 (Continued). Fungal Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medications/co-infections | Type of Infection; Method of detection | Outcome |
|-----|----------------------|------|------------------------------|-----------------------------------------|---------|
| 155 | 39 M- CD Japan       | IFX (5 infusions) | n/a                          | Asymptomatic pulmonary cryptococcosis; Histological detection | No treatment; Asymptomatic |
| 156 | 35 M- CD Japan       | IFX (8 infusions) | Mesalazine and prednisolone  | Possible pulmonary cryptococcosis; Bronchoalveolar lavage fluids antigen detection; Serum antigen negative | Fluconazole; Resolution of symptoms despite IFX continuation |
| 157 | 53 M- CD USA         | IFX over 3 years | Prednisolone and azathioprine| Cryptococcus neoformans colitis; Staining for encapsulated yeast Cryptococcus spp positive; Serum and cerebrospinal fluid antigen detection; Culture | Amphotericin B deoxycholate and 5-flucytosine; Liposomal amphotericin B substituted for amphotericin B deoxycholate due to acute renal failure; Treatment switched to fluconazole; Resolution of symptoms |
| 158 | 54 M- CD, ankylosing spondylitis France | ADM over 13 months | Prednisone and azathioprine | Pulmonary C. neoformans Culture | Liposomal amphotericin B and 5-fluorocytosine, switched to fluconazole, Resolution of symptoms |
| 159 | 26 M- CD Spain       | IFX (2 infusions) | Azathioprine                 | C. glabrata Culture | Amphotericin B and voriconazole Resolution of symptoms |
| 161 | 52 M- CD Canada      | IFX over 6 years | Budesonide and 6-mercaptopurine | A. graevenitzii Culture | Penicillin G and clarithromycin Resolution of symptoms |
| 162 | 69 M- UC USA         | IFX (1 infusion) | Azathioprine, mesalazine and corticosteroids | Bacillus dermatitidis Transbronchial lung biopsy Culture | Liposomal amphotericin B and itraconazole Resolution of symptoms; Death from myocardial infarction |

Continue ……
### Table 3 (Continued). Fungal Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of detection | Outcome |
|-----|---------------------|------|-----------------------------|----------------------------------------|---------|
| 163 | 50 M- CD USA        | IFX over 4 months, then ADM | Mesalazine, 6-mercaptopurine and hyoscyamine | C. immitis Serology: IgM and IgG antibodies positive in CSF Lung leg biopsies positive Histological examination Culture | Broad-spectrum antimicrobials Fluconazole and amphotericin B liposomal complex; Death from disseminated coccidioidomycosis |

ADM: adalimumab; CD: Crohn's disease; F: female; IFX: infliximab; M: male; TR-SMX: Trimethoprim-sulfamethoxazole; UC: ulcerative colitis

### Table 4. Viral Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of Detection | Outcome |
|-----|---------------------|------|-----------------------------|----------------------------------------|---------|
| 167 | 28 F- CD Japan      | IFX (1 infusion) | n/a | Acute hepatitis caused by HBV reactivation: AST 64 IU/L and ALT 43 IU/L; Genetic detection (4.5 log genome equivalent/mL) | No treatment Resolution of symptoms |
| 168 | 43 F- CD Japan      | IFX (6 infusions) | 6-mercaptopurine Chronic HBV; positive HBsAg, anti-HBe antibodies and anti-HBc antibodies Lamivudine prophylaxis | HBV reactivation; Genetic detection (5.4 log genome equivalent/mL) after 4th infusion AST 145 IU/L and ALT 239 IU/L after 6th infusion | Lamivudine Resolution of symptoms Continue ……….. |
Table 4 (Continued). Viral Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of Detection | Outcome |
|-----|----------------------|------|-----------------------------|----------------------------------------|---------|
| 169 | 34 M- CD Spain       | IFX (1 dose) | Azathioprine HBV infection determined after reactivation in archival serum, positive HBsAg, HBeAg, IgG anti-HBc antibodies, and HBV DNA | Acute hepatitis caused by HBV reactivation: ALT 2089 IU/L, AST 1561 IU/L, ALP 540 IU/L, γ-GTP 165 IU/L and total bilirubin 1.7 mg/dLHBsAg, IgG anti-HBc antibodies and HBeAg positive, and negative anti-HBs antibodies, IgM anti-HBc antibodies, anti-HBe antibodies | Seroconversion from HBeAg to anti-HBe antibodies HBsAg cleared HBV DNA undetectable Resolution of symptoms. |
| 169 | 38 M- CD Spain       | IFX (3 doses) | Azathioprine and metronidazole | Hepatic failure with ascites caused by HBV reactivation: ALT 2225 IU/L, AST 2146 IU/L, γ-GTP 227 U/L, total bilirubin 24.1 mg/dL HBeAg and IgM anti-HBc antibodies positive | Death from variceal bleeding, encephalopathy, hepatorenal syndrome. |
| 170 | 54 M- CD USA         | IFX over 2 years | Azathioprine and prednisone Chronic HBV | Fulminant hepatic failure caused by HBV reactivation AST 143 U/L, ALT 124 U/L and bilirubin 2.7 mg/dL; HBsAg and HBeAg positive; IgM anti-HBc antibodies subsequently positive | Lamivudine Death from stage 4 hepatic encephalopathy, jaundice, hepatorenal syndrome and hemodynamic instability. of symptoms Continue ….. |
Table 4 (Continued). Viral Infections in anti-TNF-treated IBD Patients

| Ref.  | Patient Demographics | Drug                  | Co-medication/co-infections | Type of Infection; Method of Detection                                                                 | Outcome                           |
|-------|----------------------|-----------------------|-----------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|
| 171   | 50 M- CD             | IFX (3 infusions)     | Azathioprine, Mirtazapine, pantoprazole, brotizolam | Subfulminant hepatitis caused by HBV reactivation; ALT 983 IU/L, AST 413 IU/L, \( \gamma \)-GTP 109 IU/L, LDH 237 IU/L and bilirubin 2.17 mg/dL; HBsAg, anti-HBc- and HBe-antibodies positive, and negative HBeAg and IgM anti-HBc antibodies; Genetic detection (>2.2 × 10^8 copies/mL) | Lamivudine Progressing to mild hepatic encephalopathy Eventual resolution |
|       | Austria              |                       | Previously unknown HBV carrier, with positive HBsAg and low viral load in archival serum |                                                                 |                                                                                 |
|       | Baseline HBV status unknown |                      |                             |                                                                 |                                                                                 |
| 172   | 58 F- UC             | IFX over 1 year       | Prednisone, then azathioprine | Chronic HBV infection was presumed after reactivation | Entecavir Resolution of symptoms |
|       | Spain                |                       |                             |                                                                 |                                                                                 |
|       | Baseline HBV status unknown |                      |                             |                                                                 |                                                                                 |
| 173   | 34 M- CD             | IFX over 7 months     | Azathioprine               | No treatment                                               | No treatment Resolution of symptoms |
|       | Spain                |                       |                             |                                                                 |                                                                                 |
|       | Baseline HBV status not assessed |                      |                             |                                                                 |                                                                                 |
| 174   | 41 F- CD             | IFX over 2 years      | Prednisone, Baseline HBsAg negative, anti-HBc, anti-HBe antibodies not assessed, transaminases within limit | HBV reactivation: AST 6 × ULN, ALT 10 × ULN; bilirubin 1.5 mg/dL; HBsAg, anti-HBe antibodies and IgM anti-HBc antibodies positive, and negative HBeAg | Lamivudine Initial exacerbation followed by eventual resolution of symptoms |
|       | Italy                |                       |                             |                                                                 |                                                                                 |
|       | Baseline HBV status thought to be negative |                      |                             |                                                                 |                                                                                 |
| 207   | 63 F- CD             | IFX (1 infusion)      | Corticosteroids and azathioprine | CMV hemorrhagic ileocolitis with impaired cerebral function | Foscarnet, ganciclovir metronidazole, ciprofloxacin Resolution of symptoms |
|       | Switzerland          |                       |                             | Colonoscopy Biopsy; IgM positive                           |                                                                                 |
|       |                       |                       |                             |                                                                 |                                                                                 |
|       |                       |                       |                             |                                                                 |                                                                                 |
|       |                       |                       |                             |                                                                 |                                                                                 |
### Table 4 (Continued). Viral Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of Detection | Outcome |
|-----|----------------------|------|----------------------------|---------------------------------------|---------|
| 208 | 22 M- CD USA         | IFX for 4 months | 6-mercaptopurine | CMV ileocolitis and hemophagocytic syndrome; Biopsy immunostaining positive IgM and IgG positive; Generic detection (134000 copies/mL) | Ganciclovir Splenectomy for splenomegaly Resolution of symptoms |
| 209 | 9 M- CD USA          | IFX   | 6-mercaptopurine | Sickle cell anemia | CMV colitis and multiorgan failure, IgM and IgG positive Colon biopsy, Immunohistochemistry staining | Vancomycin ticarcillin-clavulanate; ganciclovir Death from respiratory and hepatic failure Ganciclovir Resolution of symptoms |
| 210 | 45 F- CD USA         | IFX for 1 year | 6-mercaptopurine and prednisone; Evo-thyroxine replacement for Sheehan syndrome | CMV hepatitis; Paraffin immunoperoxidase staining positive IgM and IgG positive | Ganciclovir Resolution of symptoms |
| 212 | 26M- CD USA          | IFX (9 days after 1st dose) | 6-mercaptopurine, mesalazine and corticosteroids | Primary VZV Direct fluorescent antigen positive Streptococcus Culture | Acyclovir Death due to fulminant hepatic failure, disseminated intravascular coagulation, respiratory failure and oliguric renal failure Valacyclovir and acyclovir Resolution of symptoms |
| 213 | 12 F- CD USA         | IFX for 2 years | Methotrexate and prednisone | Primary VZV Direct fluorescent antigen positive VZV reactivation | Valacyclovir and acyclovir Resolution of symptoms |
| 214 | 14 M- CD USA         | IFX for 6 months | Hydrocortisone and 6-mercaptopurine | Direct fluorescent antigen positive VZV reactivation | Aciclovir Resolution of symptoms |
| 215 | 12 F- UC Italy       | IFX (7 infusions over 10 months) | Mesalazine and azathioprine | Herpes zoster followed by Henoch-Schönlein purpura | Valacyclovir Resolution of symptoms |
| 216 | 20 M- CD Portugal    | IFX (7 infusions over 10 months) | n/a | VZV reactivation Genetic determination | Valacyclovir Resolution of symptoms |

Continue............
### Table 4 (Continued). Viral Infections in anti-TNF-treated IBD Patients

| Ref | Patient Demographics | Drug | Co-medication/co-infections | Type of Infection; Method of Detection | Outcome |
|-----|----------------------|------|----------------------------|--------------------------------------|---------|
| 216 | 36 F- CD Belgium     | IFX over 5 months | n/a | Herpes zoster | Aciclovir Resolution of symptoms |
| 217 | 51- F Rectocolitis Belgium | IFX over 8 years | Prednisone; Previous exposure to IFX | VZV reactivation with meningitis Genetic detection | Ayclovir, then valacyclovir Slow recovery, with final outcome not reported |
| 218 | 38 M- CD China       | IFX (12 infusions) | n/a | Herpes zoster | Ganciclovir, potassium-sodium dehydroandroan Resolution of symptoms |
|     | 43 F- CD China       | IFX (1 infusion)  |     |             | Resolution of symptoms |
| 219 | 45 F- CD USA         | IFX (1 infusion)  | Azathioprine, prednisone | VZV manifesting as shingles | Treatment not specified Resolution of symptoms |
|     | 25 F- CD USA         | IFX (3 infusions) | Azathioprine | VZV manifesting as chickenpox |
|     | 17 F- CD USA         | IFX (2 infusions) | Azathioprine, prednisone | VZV manifesting as shingles |
| 220 | 29 F- CD France      | IFX over 2 years  | n/a | Herpes zoster | Vancomycin Resolution of symptoms |
|     | 25 F- CD France      | IFX over 4 years  |     | Herpes zoster with lumbar presentation | Resolution of symptoms |
|     | 39 M- CD France      | IFX over 36 weeks |     | Herpes zoster with dorsal presentation | Aciclovir Resolution of symptoms |
|     | 33 M- CD France      | IFX               |     | Herpes zoster with cervical multi-metameric presentation | Vancomycin, aciclovir; Resolution of symptoms |

ADM: adalimumab; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CD: Crohn's disease; CMV: cytomegalovirus; F: female; HBV: hepatitis B virus; HBeAg: extracellular hepatitis B virus core antigen; HBsAg: hepatitis B virus surface antigen; IFX: infliximab; M: male; γ-GTP: γ-glutamyl transpeptidase; TR-SMX: Trimethoprim-sulfamethoxazole UC: ulcerative colitis; ULN: upper limit of normal; VZV: varicella zoster virus
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