**Infliximab: A Review of Its Use in the Treatment of Inflammatory Bowel Disease**

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**Abstract:** Infliximab is a chimeric monoclonal antibody against anti-tumour necrosis factor alpha that has changed the management of inflammatory bowel diseases. Our review describes its mean clinical and pharmacological features, in order to resume its efficacy in induction and maintenance of clinical remission in both Crohn’s Disease and Ulcerative Colitis. Although its efficacy in induction and maintenance of remission has been established by several clinical trials, the administration of Infliximab is also associated with an increased risk of side effects, in particular in long-term treatment. We also discussed about issues regarding the correct timing to start and to stop biological therapy.

**Keywords:** Infliximab, Crohn’s Disease, Ulcerative Colitis
Introduction
Crohn’s Disease (CD) and Ulcerative Colitis (UC) are chronic intestinal inflammatory disorders characterized by a relapsing course. The etiology of these disorders is not known. There is a growing body of evidence suggesting that chronic bowel inflammation is a result of abnormalities of the mucosal immune system with an imbalance between pro-inflammatory and anti-inflammatory mediators. Therefore, medical therapy is often geared towards modulating the immune and inflammatory response. The current goals of therapy in IBD include the induction and the maintenance of corticosteroid-free remission, the promotion of mucosal healing and the prevention of complications.

Commonly prescribed therapies for IBD include corticosteroids, 5-amino-salicylate formulations, antibiotics and immunosuppressive agents (such as thiopurines, methotrexate and calcineurin inhibitors). Corticosteroids are the main treatment for the induction of remission in both moderate-to-severe UC and CD. Unfortunately corticosteroids are ineffective in maintaining remission and are associated with significant side effects when used for longer periods of time. There is less evidence supporting the use of antibiotics for the therapy of IBD, with the exception of a few settings including the treatment of perianal disease, the prevention of postoperative recurrence in CD and pouchitis. Thiopurines are effective steroid-sparing medications and are used for long-term maintenance therapy in IBD, whereas their use as monotherapy for the induction of remission is not recommended due to their slow onset of action. Cyclosporine is a calcineurin inhibitor mainly used as an induction therapy in severe colitis, but its use is limited to patients who can assume thiopurines as long-term maintenance therapy.

Over the last few years, advances in understanding the pathogenesis of IBD have led to the availability of several biological drugs that have modified the management of these disorders, especially in patients who have not responded to conventional treatments or who have become corticosteroid-dependent. Laboratory and clinical data have implicated tumour necrosis factor-alpha (TNFα) as a pivotal mediator of the inflammatory response in patients affected by IBD. Therefore, antibodies directed toward TNFα have received a great deal of attention. Infliximab, a chimeric monoclonal antibody directed against TNFα, has modified the therapeutic approach to patients with IBD. This therapy is effective in inducing and maintaining remission. This paper will review the pharmacological and clinical properties of infliximab and its efficacy and safety in the management of patients with both CD and UC.

Mechanism of Action, Metabolism and Pharmacokinetic Profile
Although the pathogenesis of IBD is not yet completely understood, several studies suggest that an altered immune response to luminal antigens leads to an exaggerated activation of both the innate and adaptive immune response, driving one of the principal mechanisms of bowel inflammation. In particular, there is a dysregulation between effector T cells (Th1, Th2, Th17) and regulatory T cells (Th3, Tr) in IBD patients, which results in a chronic tissue damage.1

Tumor necrosis factor (TNFα) is a pro-inflammatory cytokine that plays a pivotal role in this altered immunological response. This molecule is a 26 kDa transmembrane protein with an intracellular dominion, which is cleaved by the metalloproteinase TNF converting enzyme (TACE). TNFα is then secreted as a 17 kDa soluble protein, that creates trimers interacting with two different receptors, the p55 TNF receptor and the p75 TNF receptor. TNFα stimulates the release of other pro-inflammatory cytokines, such as IL-1 and IL-6, leading to expression of adhesion molecules by endothelial cells and leucocytes, facilitating leucocytes migration. It is also responsible for leucocytes activation, expression of acute-phase proteins and metalloproteinases production.2

Infliximab is an anti-TNFα chimeric monoclonal antibody (IgGκ) composed of 75% human sequence and 25% murine sequence, that specifically binds soluble and membrane-bound TNFα, forming large antibody/TNFα complexes of 2,727 kDa molecular weight. Infliximab is used in the treatment of several diseases, including rheumatoid arthritis, psoriasis, ankylosing spondylitis and IBD. The recommended dose used in IBD patients is 5 mg/kg administered intravenously for both induction and maintenance scheduled therapy. Pharmacokinetic studies showed that single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of Infliximab have increased both the maximum serum concentration (Cmax) and the
area under the concentration-time curve (AUC) in a dose-proportional way. The volume of distribution at steady state (median Vd equal to 3.0–4.1 liters) was achieved independent from the administered dose, showing that Infliximab is mainly distributed in the vascular compartment. At the single doses of 3, 5 or 10 mg/kg, the median Cmax values were 77, 118 and 277 micrograms/ml, respectively. The median terminal half-life at these doses was between 8 and 9.5 days. After the recommended single maintenance dose of 5 mg/kg for CD and 3 mg/kg for rheumatoid arthritis every 8 weeks, Infliximab could be detected in the serum of patients for at least 8 weeks. Serum levels of Infliximab were similar among adult and children patients affected by CD. In CD pediatric patients, Infliximab half-life, at the dose of 5 mg/kg, is 10.9 days. The Infliximab elimination pathway has not been clearly identified. Its clearance is likely accomplished through degradation by unspecific proteases. Not-degraded Infliximab has not been recovered in urine.

Infliximab’s mechanism of action is not clearly understood. The neutralization of TNF, the ability to fix complement and lyse cells expressing membrane-bound TNFα, as well as inhibition of other pro-inflammatory triggers seem to be its principal therapeutic effects. Immunohistochemical studies revealed that the mucosal architecture in IBD patients returned to normal after 4 weeks of Infliximab therapy with a disappearance of the neutrophils and a global reduction of CD4+ and CD8+ T lymphocytes and CD68+ monocytes. Furthermore, the percentage of intercellular adhesion molecule 1, lymphocyte function-associated antigen 1-expressing and IL-4 and TNF-positive lamina propria mononuclear cells significantly decrease. Several studies have suggested that Infliximab reduces inflammation by preventing the signalling of TNFα receptors on the cell surface, inducing cell apoptosis. Infliximab may induce monocyte apoptosis through a dose-dependent mechanism, activating members of the caspase-family and resulting in a rapid and specific increase in apoptosis of T lymphocytes in the gut mucosa. Moreover, Infliximab appears to bind peripheral blood lymphocytes and lamina propria T cells and subsequently induce apoptosis of activated lymphocytes. In vitro studies, comparing mechanisms of action of different anti-TNFα formulations, confirm the ability of infliximab and adalimumab to increase the proportion of cells undergoing apoptosis in contrast with certolizumab pegol, suggesting that other mechanisms are also involved for the efficacy of anti-TNF therapy in CD. Other in vivo studies suggest that the mechanism of action of infliximab is through the induction of caspase-dependent apoptosis.

### Clinical Studies

In the Europe and the USA, infliximab is the only anti-TNFα agent licensed for the treatment of both CD and UC. Moreover, it’s the only biological agent authorized for therapy of children suffering from CD. In the last thirteen years, several studies have supported the efficacy of this drug for both induction and maintenance of remission in IBD.

### Crohn’s Disease

The first clinical trial of Infliximab in CD was a pivotal study published in 1997 by Targan et al. This work documented that a single infusion of Infliximab was an effective induction treatment for patients with moderate to severe CD resistant to standard treatment. One hundred and eight patients with moderate to severe CD were randomized to receive a single intravenous infusion of 5, 10 or 20 mg/kg of Infliximab. At four weeks, 81%, 50% and 64% of patients receiving, respectively, 5, 10 or 20 mg/kg of Infliximab obtained a clinical response (the primary end point), defined as a reduction of 70 or more points in the score of Crohn’s Disease Activity Index (CDAI), compared with 17% of patients receiving placebo (P = 0.001). Moreover, remission, defined as a score below 150 on the CDAI, was obtained in 33% of patients given Infliximab versus 4% of patients given placebo (P = 0.005). The difference in the rates of clinical response between the Infliximab and the placebo groups remained significant through the 12 weeks of follow-up (41% versus 12%, P = 0.008). In initial smaller clinical trials, infliximab was found to reduce corticosteroid requirements but patients did relapse after a single infusion of Infliximab. In the ACCENT I trial, the authors aimed to assess the efficacy and safety of repeated infusions of Infliximab in patients who improved after an initial infusion. In this multicenter, double-blind, randomized, placebo-controlled trial 573 patients with moderate to severe luminal CD, with a score on the CDAI between 220–400, received a 5 mg/kg infusion of...
Infliximab at week 0. Three hundred and thirty-five (58%) of those who showed a clinical response (CDAI reduction of 70 or more points and a 25% or more reduction in CDAI score from baseline) were randomly assigned to subsequent infusions, at week 2 and 6 and then every 8 weeks until week 46, of placebo (group I), 5 mg/kg Infliximab (group II), or 5 mg/kg Infliximab at weeks 2 and 6 followed by 10 mg/kg thereafter (group III). Throughout follow-up, patients assigned to continued active treatment showed a greater therapeutic benefit than patients retreated with placebo. At week 30, the percentage of responders at week 2 in remission (co-primary endpoint) was higher in both groups II and III (39% and 45%; $P = 0.003$ and $P = 0.0002$, respectively) than in group I (21%). Similar results were seen at week 54. Moreover, patients who received maintenance Infliximab infusions (group II and III) had a significantly longer time to loss of response up to week 54 (co-primary endpoint; $P = 0.002$ and $P = 0.0002$, respectively) and were more likely to discontinue corticosteroids ($P = 0.004$) than patients treated with placebo (group I). This steroid-sparing effect of infliximab is an important treatment advance in the management of CD.

Rutgeerts et al reported an analysis of CD patients treated with Infliximab in ACCENT I comparing episodic and scheduled treatment strategies under conditions that simulate clinical practice. After administration of a single infusion of 5 mg/kg of Infliximab (week 0), patients were stratified to infusions of placebo (episodic strategy) at week 2, 6 and every 8 weeks until week 46, infliximab 5 mg/kg at weeks 2, 6 followed by 5 mg/kg every 8 weeks (5 mg/kg scheduled strategy), or infliximab 5 mg/kg at weeks 2, 6 followed by 10 mg/kg every 8 weeks (10 mg/kg scheduled strategy). Open label treatment with infliximab 5 mg/kg or higher was offered beginning at week 14 for loss of response. The primary focus of this analysis was to provide clinically relevant data with an emphasis on CDAI scores and clinical remission. The scheduled infliximab groups, especially the 10 mg/kg group, showed significantly lower CDAI scores from weeks 10 to 54, and higher response and remission rates from weeks 10 to 30 compared to the episodic infliximab group. Both scheduled groups had fewer hospitalizations, higher rates of mucosal healing and fewer subjects developed antibodies compared to those in the episodic group. There was no increase in the number of side effects in the scheduled groups.

Infliximab has also been shown to be an effective treatment for fistulizing CD. Closure of fistulas is rare in patients with CD who are receiving standard therapy. Several antibiotics have been used for the healing of fistulas in CD, but their efficacy has not been established in controlled clinical trials. Immunosuppressive agents are only marginally effective in the treatment of fistulizing CD. Present et al evaluated the efficacy of Infliximab in healing CD enterocutaneous fistulas in 94 patients: 62% of patients treated with three infusions induction regimen (5 mg/kg or 10 mg/kg) obtained a reduction of 50% or more from baseline in the number of open fistulas at two or more consecutive visits (primary endpoint) compared to 26% of patients treated with placebo ($P = 0.002$ and $P = 0.02$, respectively). In addition 46% of patients had closure of all draining fistulas at 18 weeks after the three infusions of Infliximab compared to 13% of patients receiving placebo ($P = 0.001$ and $P = 0.04$, respectively).

The ACCENT II study, the largest placebo-controlled trial examining the efficacy of Infliximab for the treatment of perianal and enterocutaneous fistulizing CD, also found that long-term therapy with Infliximab is more effective than the short-term therapy. This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated Infliximab maintenance therapy in patients with CD and one or more draining abdominal or perianal fistulas. Three hundred six adult patients were treated with Infliximab 5 mg/kg at weeks 0, 2 and 6. At week 14, those with a response (defined as a reduction of at least 50% from baseline in the number of draining fistulas), were randomly assigned to receive an infusion of either placebo maintenance or 5 mg/kg Infliximab maintenance, every 8 weeks and to be followed up to week 54. Patients assigned to receive Infliximab maintenance therapy had a significantly longer time to loss of response (primary endpoint) than those who received placebo (more than 40 weeks versus 14 weeks; $P < 0.001$). At week 54, 19% of patients in the placebo group had a complete absence of draining fistulas as compared with 36% of patients in the Infliximab group ($P = 0.009$). Furthermore, Infliximab has been shown to improve quality of life and reduce fistulizing CD-related hospitalizations and surgery.
in patients undergoing systematic maintenance therapy.20

Recently, results from the REACH study supported the efficacy of Infliximab for the treatment of CD in children and confirmed the superiority of an interval maintenance therapy regimen every 8 weeks. This study evaluated the safety and efficacy of Infliximab in children with moderately to severely active Crohn’s disease. At week 10, 99 of 112 (88.4%) patients responded to Infliximab (5 mg/kg) and 66 of 112 (58.9%) patients achieved clinical remission. At week 54, 63.5% and 55.8% of patients treated with Infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 33.3% and 23.5% of patients receiving treatment every 12 weeks ($P = 0.002$ and $P < 0.001$, respectively).21

During recent years, there has been great debate regarding the appropriate time to introduce different therapies in the course of IBD, and particularly in CD. With regard to the classic therapeutic strategy (“step up”), a progressive introduction of more aggressive treatments as the severity of the disease increases has been advocated. For example, a CD patient with mild-to-moderate activity might be treated with sulfasalazine or budesonide, while a patient with moderate-to-severe disease might receive systemic steroids to induce remission, followed by maintenance therapy with a thiopurine. Infliximab and other anti-TNFα therapies are considered as an option only if traditional approaches are not enough to avoid a relapse of the disease. Conversely, the “top down” strategy is based on the early identification of CD patients who are more likely to have a disabling course of their disease and on the early treatment of these patients with biological therapies and immunomodulators.22

Several trials have shown that early treatment of CD with immunomodulators and anti-TNFα agents leads to superior clinical outcomes, including healing of the intestinal mucosa. In one such study, a total of 133 corticosteroid naïve patients with recent onset CD were randomized to initial therapy with Infliximab and azathioprine, or to corticosteroids and, eventually, later azathioprine. At week 26, 60% of patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 40% of controls, for an absolute difference of 24.1% ($P = 0.006$). Corresponding rates at week 52 were 61% and 42% (absolute difference 19.3%, $P = 0.028$). Also endoscopic healing was higher using the top-down approach (week 104: 73% versus 30%; $P = 0.0028$).23

A prospective 2-year follow-up of this trial has shown that complete mucosal healing at week 104 was the only factor that predicted sustained corticosteroid-free remission up to 4 years after therapy was started ($P = 0.036$; OR 4.35, 95% CI 1.1–17.2).24

A head to head comparison of Infliximab with or without azathioprine was the subject of the SONIC trial. The SONIC study compared 3 different treatments (Infliximab monotherapy, azathioprine monotherapy and the combination of the 2 drugs) for induction and maintenance of remission in 508 patients affected by moderate-severe CD who had not undergone previous immunosuppressive or biological therapy. At 26 weeks the corticosteroid-free remission rate (primary endpoint) in patients receiving combined immunosuppressive therapy with Infliximab and azathioprine were higher than with the Infliximab monotherapy (57% versus 44%, $P = 0.02$). The remission rate for combination therapy was also higher than in patients with azathioprine monotherapy (57% versus 30%, $P < 0.001$; 44% versus 30%, $P = 0.006$, respectively). Similar numerical trends were found at week 50. The SONIC trial also found that the early use of an infliximab-based strategy improved mucosal healing at week 26 (44% combination therapy and 30% Infliximab monotherapy versus 16% azathioprine monotherapy; $P < 0.001$ and $P = 0.02$, respectively).25 Nevertheless, conflicting data about efficacy of Infliximab mono- versus combination-therapy26,27 and the cumulative body of evidence that suggests that combined immunosuppressive therapy may increase toxicity require additional long term safety and efficacy studies.

There are very few data currently available describing the long-term efficacy of Infliximab in CD patients. Results from a single-centre cohort have demonstrated the long-term efficacy of Infliximab therapy in a large group of patients with CD with a median follow-up of almost 5 years. Sustained benefit was observed in more than half of the patients (63%) receiving long-term treatment. In 68% of these patients, Infliximab therapy was ongoing, whereas infliximab was stopped in 32%. In this study, the
scheduled maintenance regimen was more effective than the episodic regimen for steroid withdrawal and avoidance of hospitalizations and surgery.\textsuperscript{28}

**Ulcerative Colitis**

The goals of biologic treatment in UC are induction and maintenance of remission in corticosteroid-dependent or -refractory patients with need for colectomy.\textsuperscript{29} Two large placebo-controlled trials, ACT 1 and ACT 2, demonstrated the efficacy of Infliximab in the treatment of UC. ACT 1 and ACT 2 showed that Infliximab is effective in patients who have moderate-to-severe disease despite the use of conventional therapy.\textsuperscript{30} In each trial 364 patients received placebo or Infliximab (5 mg/kg or 10 mg/kg) intravenously at weeks 0, 2, 6 and then every 8 weeks through week 46 (in ACT 1) or week 22 (in ACT 2). The primary endpoint was clinical response at week 8 and was achieved in both studies. In ACT 1 69\% of the patients treated with 5 mg/kg of Infliximab and 61\% of those who received 10 mg/kg had a clinical response at week 8, as compared with 37\% of those who received placebo (\(P < 0.001\) for both comparison with placebo); 39\% and 32\% of the patients randomized in active arms obtained clinical remission at week 8 as compared with 15\% of patients in placebo arm (\(P < 0.001\)). These significant differences in treatment arms were also observed in ACT 2: 64\% and 69\% of patients in Infliximab arms (5 mg/kg and 10 mg/kg respectively) versus 29\% in placebo arm had clinical response at week 8 (\(P < 0.001\) for both comparisons with placebo), whereas 34\% and 27\% versus 6\% achieved clinical remission (\(P < 0.001\)). Clinical response and remission were significantly maintained compared with placebo through week 30 and 54. Infliximab was also significantly more effective than placebo in inducing mucosal healing both at weeks 8, 30 and 54 (ACT 1 week 54 mucosal healing: 18\% with placebo, 45\% with 5 mg/kg and 47\% with 10 mg/kg of Infliximab, \(P < 0.001\) for both comparison with placebo; ACT 2 week 30 mucosal healing: 30\% with placebo, 46\% with 5 mg/kg and 57\% with 10 mg/kg of Infliximab, \(P = 0.009\) and \(P < 0.001\) versus placebo). Similarly, a decrease in the median daily corticosteroid doses and corticosteroid-sparing effects during 30 to 54 weeks of therapy, were greater among patients in the Infliximab groups than among those in the placebo group. Further analysis from ACT 1 and ACT 2 open-label extension phase focused on colectomy and hospitalization rates during follow-up to 54 weeks. Combined results on all patients treated with Infliximab revealed an absolute risk reduction of 7\% in the incidence of colectomy, with a cumulative incidence of colectomy of 10\% for Infliximab and 17\% for placebo (\(P = 0.02\)). Compared with placebo, fewer UC-related hospitalizations and surgeries/procedures per 100 patient-years of treatment occurred with Infliximab therapy: 40 versus 20 (\(P = 0.003\)) and 34 versus 21 (\(P = 0.03\)), respectively.\textsuperscript{31}

A systematic review demonstrated that in patients with moderate to severe UC whose disease was refractory to conventional treatment using corticosteroids and/or immunosuppressive agents, three Infliximab induction-doses were more effective than placebo in inducing clinical remission(RR3.22, 95\%CI2.2–4.8), endoscopic remission (RR 1.88, 95\% CI 1.5–2.3) and clinical response (RR 1.99, 95\% CI 1.7–2.4) at 8 weeks. A single infusion of infliximab was also more effective than placebo in reducing the need for colectomy within 90 days after infusion (RR 0.44, 95\% CI 0.22 to 0.87).\textsuperscript{32}

Another meta-analysis evaluated Infliximab therapy in UC, with heterogeneous results. Mean short-term (2.3 weeks) response and remission with Infliximab were 68\% and 40\%, respectively. Mean long-term (8.9 months) response and remission were 53\% and 39\%, respectively. In this meta-analysis, infliximab was superior to placebo for all endpoints (short-/long-term response/remission): ORs from 2.7 to 4.6, and number-needed-to-treat (NNT) from 3 to 5.\textsuperscript{33}

Similar to the debate regarding combination therapy in CD, it has not been determined if infliximab should be used as monotherapy or in combination with an immunosuppressive agents for the treatment of UC. Subgroup analyses of the ACT trials and data from a single center retrospective study, suggest that there is no significant added benefit using concomitant immunosuppressant therapy compared to monotherapy with infliximab.\textsuperscript{27,34}

Infliximab has also been evaluated as a rescue therapy in hospitalized patients with severe UC not responding to intravenous corticosteroids. A small number of case series have reported success using infliximab in this settings.\textsuperscript{35–37} Only one randomized placebo-controlled trial has been published.\textsuperscript{38} In this study, forty-five patients with moderate to severe acute attack of UC were included and randomized
to Infliximab or placebo 4 days after initiation of corticosteroid treatment. The primary end point was colectomy or death 3 months after randomization. Significantly more patients in the placebo group (14/21) than in the Infliximab group (7/24) had a colectomy ($P = 0.017$; OR 4.9; 95% CI 1.4–17), without any death occurrences. In a separate multicentre uncontrolled trial, infliximab re-infusion was more effective than a single infusion for preventing early colectomy.39

Safety

The use of Infliximab causes a modulation of the immune system. This modulation may lead to both short- and long-term side effects including allergic type reactions, common and opportunistic infections, immunological disorders and malignant complications. Most of the safety data come from post-marketing surveillance including the Periodic Safety Update Report—PSUR40 and large patients’ registries such as Crohn’s Disease Therapy, Resource, Evaluation, and Assessment Tool—TREAT41 registry and the European Safety Surveillance Registry—ENCORE.42

Immunogenicity. One concern of treating patients with infliximab has been the problem of immunogenicity ascribed to the chimeric features of the drug. In fact, in some treated patients there is the development of antibodies against infliximab, that seem to be associated with a loss of the clinical response to therapy and can be responsible for acute reactions, including mild to severe clinical manifestations and delayed hypersensitivity reactions. Acute reactions can be verified within seconds or a few hours following the start of the infusion. Symptoms may include burning sensation, itching, erythema and pain. Rarely, shortness of breath, urticaria, hypotension or stridor may occur. The exact mechanism of acute reactions has not been fully elucidated, but it may be related to the presence of ATIs (IgG Antibodies To Infliximab).43 Moreover, Vultaggio et al demonstrated that in some rheumatologic patients who had infusion-related reactions IgE and IgM antibodies against infliximab are also detectable.44 A concomitant immunosuppressive therapy, such as azathioprine, may reduce ATIs formation and may improve the pharmacokinetics of infliximab.45 If an acute reaction is verified, the infusion must immediately be interrupted, followed by therapeutic procedures, if it’s necessary. Moreover, patients may be pre-treated with steroids and antihistaminic agents to prevent mild and transitory effects. Delayed hypersensitivity-like reactions are caused by development of ATIs and subsequent immune complex deposition: the main symptoms are arthralgia and muscle ache. The available data suggest an increased risk of delayed hypersensitivity in patients treated with episodic infusions with a large interval after the first administration of infliximab.45 Baert et al showed that an ATI concentration of 8.0 µg per mL or greater before an infusion predicts a shorter duration of response (35 days as compared with 71 days among patients with concentrations of less than 8.0 µg per mL; $P < 0.001$) and a higher risk of infusion reactions (RR 2.4, 95% CI 1.6 to 3.7; $P < 0.001$). Other available data obtained from this study suggest that the treatment with immunosuppressive agents prevents infusion reactions and helps to maintain the clinical efficacy.47 Furthermore, it seems that the episodic treatment increases the risk of ATI formation compared to the scheduled maintenance treatment, improving the efficacy and the tolerance, as demonstrated in the ACCENT I study. The antibodies to Infliximab were detected in 30%, 10% and 7% of group I (placebo), II (5 mg/kg) and III (10 mg/kg), respectively ($P < 0.0001$).48 Recently, new techniques were introduced for the measurement of antibodies to anti-TNFα agents, that may be used as a biomarker for treatment adjustment. The large number of treated patients, in combination with these new assays, may modify therapeutic approaches to IBD.49

Infections. The immunosuppressive effect of infliximab leads to an increased risk of infections during therapy. Most commonly, these infections come from urinary or respiratory tract and are easy to treat. Other serious infections, including sepsis, pneumonia, systemic tuberculosis or opportunistic infections (eg, Pneumocystisiosis, Listeriosis, Hystoplasmosis, Candidosis, Aspergillosis) have been reported after the use of infliximab. The reactivation of latent tuberculosis as active extrapulmonary or disseminated tuberculosis is a serious event described during Infliximab therapy;50 it is currently well known that the treatment with anti-TNFα agents may predispose to a significant increase in tuberculosis reactivation.51 Therefore, screening for tuberculosis is strongly recommended before initiating therapy with an
anti-TNFα. Tuberculin skin test (PPD), Interferon-gamma release assays (IGRAs) and chest-X ray are the screening tests currently used to detect latent or active Mycobacterium tuberculosis infection. Patients with latent infection, meaning positive PPD and IGRAs or positive chest-X ray without evidence of active disease, should be treated with the prophylactic therapy before starting Infliximab. It is generally recommended that the treatment with Infliximab should begin at least one month after starting chemoprophylaxis with isoniazid. Infliximab should not be administered in cases of active tuberculosis infection.52 The reactivation of viral diseases, such as hepatitis B and C, may also be possible. The available data on HBV infection in patients treated with infliximab are limited to very few case reports about IBD and rheumatologic patients: a reactivation of chronic HBV infection occurred in some of them. In HbsAg-positive patients with HBV-DNA < 20000 IU/ml, the chemoprophylaxis with antiviral agents, such as lamuvudine, should be considered to reduce the potential risk of HBV reactivation; on the other hand, in HbsAg-positive patients with HBV-DNA > 20000 IU/ml, the active infection should be treated and then the anti-TNFα therapy should be re-considered. About the HCV infection, there is no evidence that Infliximab worsens the course of this chronic hepatitis, but long-term data are not available. Therefore, IBD patients who are candidates for biological treatment should be screened for HBV and HCV infection and normal liver function tests should be demonstrated before undergoing infliximab therapy.52 Patients should also be screened for perianal and intra-abdominal infections or abscesses, which contraindicate biological treatments. Data about invasive fungal infections during infliximab treatment are limited: MEDLINE and pubmed databases (from 1966 to 2007) documented 226 cases associated with infliximab, but out of which 16 patients with IBD were reported.53 According to these evidences, other long-term safety data during infliximab treatment and concomitant therapies are needed. At present, most of long-term safety data about Infliximab in CD patients come from the TREAT Registry: 6290 subjects with CD were enrolled, 3179 out of which received Infliximab and 3111 received other therapies for a mean follow-up of 1.9 years. The mortality rate was similar among the two groups. After an adjustment for confounding factors including disease severity and treatment with other immunosuppressive drugs, the risk of serious infections during infliximab therapy was similar to that observed with the use of conventional immunomodulators. On the other hand, the disease severity and the use of steroids or narcotics were associated with a significantly increased risk of serious infections.41 The ENCORE study is a prospective, observational, postmarketing safety surveillance registry of CD subjects treated with infliximab or other standard therapies. In this study, the authors reported data about the first 2008 patients who were enrolled (1166 out of which received infliximab) in this surveillance registry. The median follow-up was about 13 months and there were no new safety reports. However, the overall incidence of adverse events was slightly higher in the infliximab-treated group (54% vs. 41%), including a slightly higher rate of serious infections (2.8% vs. 1.7%).42 If the TREAT and the ENCORE results did not show a strength risk of infections with Infliximab, other clinical trials demonstrated that number of infections is higher especially if anti-TNFα is associated to immunosuppressive agents or corticosteroids. Torunen et al identified the risk factors of opportunistic infections in 100 IBD patients. In univariate analysis, the use of corticosteroids (OR 3.4, 95% CI 1.8–6.2), thiopurines (OR 3.1, 95% CI 1.7–5.5) and infliximab (OR 4.4, 95% CI 1.2–17.1) were individually associated with a significantly increased odds for opportunistic infections. The multivariate analysis showed that the use of only one of these drugs yielded an OR of 2.9 (95% CI 1.5–5.3), whereas the combined use of 2 or 3 drugs yielded an OR of 14.5 (95% CI 4.9–43) for opportunistic infections.54 Schneeweiss et al examined the safety of Infliximab comparing the rate of serious bacterial infections in Crohn’s patients treated with Infliximab, steroids or immunosuppressants. The authors identified from linked health care utilization databases in British Columbia nearly 11500 patients and 16699 treatment episodes with one of these 3 drug classes. A total of 104 serious bacterial infections requiring hospitalization were identified. The risk for infection was higher in patients treated with multiple agents, including Infliximab and steroids (RR 1.4, 95% CI 0.6–3.5). Moreover the combination of Infliximab with an immunosuppressive agent increased the risk twice
over (RR 2.4, 95% CI 1.2–4.9). Steroids alone also seemed to increase the risk for infection (RR 1.6, 95% CI 0.9–2.8). Finally, infliximab alone did not seem to increase the risk for serious bacterial infections. These findings support the concept of mono-therapy when using an anti-TNFα agent.55

**Malignancies and lymphoma.** Anti-TNFα agents have changed the way of treating patients with IBD refractory to conventional medications, but safety data about these drugs indicate that they increase the risk of rare events such as malignancies and lymphoma. Some of these have been reported in studies of Infliximab-treated patients with IBD. At present, the available data do not provide a great evidence for a clear association between Infliximab and the increased cancer risk: other factors, such as the underlying chronic inflammation, the severity of the disease, concomitant medications (eg, immunomodulators) and Infliximab itself, could be, separately or in combination, risk factors for the development of these malignancies.56 In a recent meta-analysis of 21 placebo-controlled trials, there was no identified difference in the frequency of malignancies between the group of patients treated with anti-TNFαs (including Infliximab) and the control groups (0.24% versus 0.39%, respectively).57 The last available data about malignant disorders in CD patients treated with Infliximab come from the TREAT registry: Lichtenstein et al demonstrated that the incidence of cancers was similar in Infliximab and non-Infliximab treated patients (0.43 versus 0.56 per 100 pt/ysrs for malignancies, RR 0.76; 0.04 versus 0.05 per 100 pt/ysrs for lymphoma, RR 0.74).58 Further confirmation resulted from an italian multicenter matched-pair study conducted on 808 CD patients (404 CD patients treated with Infliximab were matched with 404 CD patients who had never received anti-TNFα therapy): the frequency of a new diagnosis of neoplasia was comparable in the two groups (2.2% versus 1.73%, respectively; \( P = \text{ns} \)).59 Moreover, PSUR reports on Infliximab safety showed that the worldwide cancer and lymphoma percentages were 0.95 and 0.12 per 1000 patients/years, respectively; these reporting rates seem to remain relatively stable during the bi-annual analysis.40 As far as the specific risk of lymphoma is concerned, it is potentially increased with the use of anti-TNFα drugs, especially when in combination with immunosuppressants. Siegel et al performed a meta-analysis to determine the rate of non-Hodgkin’s lymphoma (NHL) in adult CD patients who have received anti-TNFα therapy and to compare this rate to that of a population-based registry and a population of CD patients treated with immunomodulators. Among anti-TNFα treated subjects 13 cases of NHL were reported in this study, 12 of them on Infliximab therapy. The majority of these patients had a previous immunomodulator exposure to thiopurines or methotrexate. Compared with the expected rate of NHL in the SEER (Surveillance Epidemiology End Results) database (1.9 per 10000 patient-years), anti-TNFα treated subjects had a significantly elevated risk (SIR 3.23, 95% CI 1.5–6.9). When compared with the NHL rate in CD patients treated with immunomodulators alone (4 per 10000 patient-years), the SIR was 1.7 (95% CI 0.5–7.1).60

The hepatosplenic T-cell lymphoma (HSTCL) is a rare form of peripheral T-cell lymphoma: cases of HSTCL described in medical literature include young IBD male patients treated with immunosuppressors and anti-TNFα agents. This lymphoma is associated with an aggressive clinical course, a low response to conventional therapies and an high mortality rate. A total of 22 CD patients treated with Infliximab and thiopurines, 3 of them later switched to Adalimumab, developed HSTCL.61–63 At present, it is unclear whether Infliximab or its combination with thiopurines may influence the risk of HSTCL.

**Pregnancy.** The management of pregnancy in IBD patients is an actual problem for gastroenterologists. A meta-analysis, conducted by Cornish et al, showed that IBD pregnant women have great possibilities to develop adverse pregnancy outcomes, if compared with women of general population: active disease seems to increase the incidence of prematurity, cesarean section, low birth weight and congenital abnormalities.64 These findings are confirmed also in a recent study performed in a population of Northern California: a total of 461 pregnant women with IBD were matched to 493 unexposed pregnant women. Women with IBD were more likely to have an adverse conception and pregnancy outcomes or a complication related to gestation than healthy women.55 Pregnant patients with IBD should be treated as a potentially high-risk group, selecting therapies more carefully. Infliximab is a FDA pregnancy category B drug. Infliximab does not pass the placenta during the first trimester of pregnancy, but
placental transfer is possible during the second and third trimester: Vasiliauskas et al reported a case report of a 32-year-old woman with refractory CD that continued Infliximab until 2 weeks before delivering. Six weeks after deliver, the breast-fed infant’s serum Infliximab level was 39.5 microg/mL. Serial measurements revealed a continued slow decline of the infant’s Infliximab levels during the following 6 months, without adverse events for infant. However, Infliximab was not detected in breast milk. Most of the Infliximab safety data in pregnant patients with IBD come from the TREAT registry and the Infliximab Safety Database maintained by Centocor. TREAT registry reported 36 cases of pregnancies in women with CD, with the same rate of miscarriage and neonatal complications compared to untreated patients. Centocor database suggests that Infliximab exposure during pregnancy results in outcomes that do not differ from those in the U.S. population of pregnant women and pregnant women with CD not exposed to Infliximab.

In another study, all 10 pregnancies of CD patients treated intentionally with Infliximab throughout their pregnancy ended in live births. No infants had congenital malformations, intrauterine growth retardation or small for gestational age parameters. Three infants were premature and one had low-birth weight. In conclusion, Infliximab doesn’t seem to increase the risks during a pregnancy for both the mother and the infant. Nevertheless, it is necessary to carefully appraise the use of an anti-TNFα during pregnancy, since the data are limited.

Other safety issues. Other noninfectious or malignant complications associated with Infliximab include neurologic disorders. Some reports of multiple sclerosis, demyelination and optic neuritis associated with Infliximab have been described. However, the underlying relationship between IBD and these neurologic conditions has not been established. Abnormal liver functions tests are also associated with Infliximab treatment: these abnormalities include cholestatic diseases or hepatitis-like syndromes. Worsening of congestive heart failure was reported during Infliximab therapy: for this reason its use is contraindicated in IBD patients with class III–IV NYHA congestive heart failure. Development of antinuclear antibodies against double-stranded DNA has been described in CD patients treated with Infliximab. Beigel et al analysed a cohort of IBD patients treated with anti-TNFα agents, regarding antinuclear antibodies (ANA), double-strand (ds) DNA antibodies, and the occurrence of lupus-like syndrome. Results from this study showed that dsDNA antibody levels ≥9 U/mL are associated with clinical symptoms of lupus-like syndrome. Moreover, IBD patients of higher age have an increased risk for development of ANA and lupus-like syndrome, whereas concomitant immunosuppressive therapies may have a protective effect. Vermeire et al reported two cases of drug-induced lupus erythematosus, underlying that antinuclear antibodies were associated with the female sex and skin manifestations. Furthermore, the true incidence and clinical relevance of antibodies formation is still unknown. In conclusion, only few CD patients treated with Infliximab and immunosuppressants develop antinuclear antibodies; however, this condition is not associated with autoimmune diseases in the majority of cases.

Efficacy

Induction and maintenance of clinical remission. Available data from the ACCENT I and ACCENT 2 (luminal and fistulizing Crohn’s disease pivotal trials) and the ACT 1 and ACT 2 (Ulcerative Colitis pivotal trials) demonstrated the Infliximab efficacy in rapidly achieving and sustaining clinical remission (see section of clinical studies). Few studies have been reported about the long-term outcome of Infliximab treatment for IBD in clinical practice. Such studies include small cohort of patients and a limited follow-up beyond one year. Recently, an observational study, performed by Schnitzler et al, assessed the long-term outcome of Infliximab therapy in a consecutive series of 614 patients with CD, with a median follow-up of almost 5 years. In this study, the short and the long-term response rates were higher than those reported in ACCENT I and II trials. Clinical improvement was also demonstrated not only during 1 year as in the previous published trials, but along a median follow-up of 4.6 years.

Mucosal healing. Mucosal healing has become a valuable marker of efficacy of therapy in IBD patients, predicting a favorable disease outcome. Available data come from the endoscopic evaluation of subgroups of patients in randomized controlled trials or from observational studies. In the ACCENT I trial, a significantly higher number of CD patients showed mucosal healing after scheduled Infliximab
compared with episodic treatment (44% versus 18%, \( P = 0.041 \)), suggesting a role for mucosal healing as a monitoring parameter during follow-up. Moreover, patients with mucosal healing showed a less incidence of hospitalization and surgery.\(^7\) Mucosal healing has also been reported in the assessment of Infliximab efficacy in UC: in ACT 1 and 2 trials mucosal healing occurred in significantly more patients in the Infliximab groups compared to the placebo group (\( P < 0.009 \)).\(^8\) Recent researches indicated that long-term healing of the bowel mucosa can be achieved even beyond one year of scheduled treatment with Infliximab. A significantly longer disease-free interval was shown for patients with mucosal healing, in addition to improved long-term outcome and a lesser need of major abdominal surgery among patients on long-term maintenance treatment with Infliximab.\(^9\)

**Closure of fistulae.** Infliximab has been the first drug that demonstrated to be effective for inducing closure of fistulae in patients with fistulizing CD and for maintaining clinical response for one year. The efficacy of Infliximab as maintenance therapy for patients with fistulae was examined in ACCENT II study, as explained in the previous section of clinical studies.\(^8\) Recent evidences documented that the Infliximab therapy in combination with seton drainage during the examination under anesthesia is a safe and effective short-term treatment for complex perianal CD.\(^8\)

**Steroid sparing.** Minimizing the use of corticosteroids is one of the most important therapy aims in the management of IBD patients, because of their several side effects and morbidity. In ACT I and 2 and ACCENT I trials, 56% and 51% of patients were receiving corticosteroids at baseline, respectively. The corticosteroid-sparing effect was clinically meaningful in both trials. In the ACT trials the proportion of patients who were in clinical remission and had discontinued steroids was higher in the Infliximab groups compared to the placebo groups (24% versus 10% at week 30, \( P = 0.03 \); 26% versus 9% at week 54, \( P = 0.006 \)). In ACCENT I trial, a significantly greater proportion of patients in the Infliximab scheduled regimen group had the corticosteroids tapered and remained free of steroids throughout the study (44% for 5 mg/kg group, \( P = 0.03 \); 47% for 10 mg/kg group, \( P = 0.01 \)).\(^6,17,30\) Similar results were reported in the cohort of 614 CD patients treated with Infliximab during a longer follow-up (5 years): the steroid withdrawal was possible in more than 70% of patients taking steroids at baseline. The scheduled treatment with Infliximab seemed to make able to stop steroids more frequently and earlier than the episodical treatment.\(^22\) The GETAID study, enrolling 115 patients with corticosteroid-dependent active CD, demonstrated that Infliximab plus azathioprine were significantly more effective than azathioprine alone over one year in inducing clinical remission off steroids (57% vs. 29% at week 24—primary endpoint, \( P = 0.003 \); 40% vs. 22% at week 52, \( P = 0.04 \)).\(^8\) Finally, in the SONIC study, the treatment with Infliximab, as compared with azathioprine alone, resulted in significantly higher rates of corticosteroid-free clinical remission at week 26 among patients with active CD (primary end point). The greatest efficacy was observed with the combination therapy: at week 26, 56.8% of the 169 patients receiving Infliximab plus azathioprine, 44.4% receiving Infliximab and 30% receiving azathioprine alone, were in corticosteroid-free clinical remission (\( P < 0.001 \) for the comparison with combination therapy, \( P = 0.006 \) for the comparison with Infliximab).\(^25\)

**Reduction of hospitalizations and surgeries.** Patients affected by IBD require frequent hospitalizations and surgery at some stage of their disease. Lichtenstein et al examined the effect of the Infliximab maintenance therapy on hospitalizations, surgeries and procedures in patients enrolled in the ACCENT II study. Patients who received Infliximab had significantly fewer mean hospitalization days (0.5 versus 2.5 days, \( P < 0.05 \)), mean number of hospitalizations (11 versus 31, \( P < 0.05 \)), all surgeries and procedures (65 versus 126, \( P < 0.05 \)), compared to patients who received placebo.\(^8\) Moreover, the results from a single centre cohort of 614 CD patients showed that the rates of hospitalizations and surgery were lower in patients treated with Infliximab scheduled regimen during a median follow-up of 55 months.\(^28\)

**Improvement of quality of life.** IBD symptoms, need for surgery, young age of patients, long-term treatment and high incidence of relapse may dramatically reduce patients’ quality of life. Results from the main randomized, placebo-controlled trials showed that Infliximab improves health-related quality of life in IBD patients. In the ACT 1 and 2 studies, UC subjects who achieved clinical response or remission had significantly greater improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) at week 30, compared with non responders (\( P < 0.001 \)).\(^35\) As
regards CD, there was an improvement in IBDQ score in both scheduled Infliximab groups of the ACCENT I study, although consistent statistical significance was only reached in the 10 mg/kg scheduled treatment group.\textsuperscript{17}

Place in Therapy

Infliximab has strongly improved the treatment of patients with IBD, achieving therapeutic goals such as the induction and the maintenance of corticosteroid-free remission, mucosal healing and the decreasing in the need for hospitalizations and surgeries. Its place in IBD treatment algorithms must be carefully defined, because of its uncertainly long-term safety profile and its high cost. An important question for gastroenterologists is at what point during the course of the disease Infliximab should be used. As previously mentioned in the section regarding the clinical studies, the treatment guidelines\textsuperscript{86–88} generally recommend that anti-TNF\alpha therapies should be reserved for IBD patients in whom conventional therapies have failed. As far as luminal CD is concerned, Infliximab should be considered in patients with corticosteroid-refractory or -dependent disease in combination or not with thiopurines. In complex perianal CD, recent guidelines suggest that Infliximab should be used as a first choice of medical therapy in conjunction with surgical therapy and seton placement,\textsuperscript{88} whereas other authors place anti-TNF\alpha as a second line treatment.\textsuperscript{86} As far as UC is concerned, Infliximab should be considered in patients with corticosteroid-refractory disease and corticosteroid-dependent disease who are intolerant/refractory to thiopurines.\textsuperscript{87,88} Maintenance therapy with Infliximab should be considered for up to one year in patients with response to the induction regimen, although a prolonged use over one year can be evaluated on a case-by-case basis.\textsuperscript{86–88} This therapeutic algorithm (the step-up strategy) generally advocates a stepwise treatment approach according to the disease location and the severity at presentation, resulting in a progressive increase of treatments according to the increasing severity of the disease. The step-up approach has been recently challenged by the top-down strategy, where biologics with or without immunosuppressive agents have been advocated as first-line or early treatment. This concept has gradually grown, especially for CD, in view of the fact that a significant number of patients fails to respond to traditional therapies and goes towards complications. Therefore, an aggressive treatment from the onset or early in the course of the disease may improve the outcome of the disease itself.\textsuperscript{89} The future challenge would be to identify subgroups of patients who will benefit from one or the other approach. The patients who will develop CD with a benign clinical course will probably benefit from a step-up treatment, while patients who will develop CD with a complicated course will probably benefit from a top-down approach. The ability to predict CD course is currently somewhat rudimentary and this can be mainly attributed to disease heterogeneity. Different definitions of disabling disease course have been suggested by several studies. A recent study identified the presence of perianal disease at diagnosis, young age at time of disease onset and early need for corticosteroids as independent factors associated with a disabling CD course.\textsuperscript{90} However, in clinical practice none of these factors are accurate enough to determine whether a patient will have an aggressive natural history or not. Data from clinical studies suggest that early use of Infliximab or others anti-TNF\alpha may improve patients’ outcomes and may alter the disease natural history. The clinical factors at diagnosis suggesting a poor prognosis in CD should be taken into account when determining the initial therapeutic approach. This category of patients currently appears to be the most suitable for early introduction of biologics and/or immunosuppressants.\textsuperscript{86,88} However, the benefit of an early treatment with biologics in this patient subgroup is not yet clearly demonstrated and a widespread use of a top-down approach cannot be recommended in all CD patients.

Conclusions

Infliximab therapy has changed the management of IBD patients and has improved the goals of therapy. In the last years, several clinical studies have been carried out in order to value its efficacy and safety profile as described in this review, but additional long-term safety data are required. Many issues regarding e.g. the timing, the treatment duration, the association or not with immunosuppressants and the personalized therapy still remain to be answered. Although
these questions need to be clarified. Infliximab seems remarkably effective in selected patients improving the natural course of IBD.

Disclosure
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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