Research Review
PRODUCT REVIEW

Infliximab (REMICADE®)

This review discusses the evidence in support of the use of infliximab (REMICADE®), a chimeric monoclonal antibody against tumour necrosis factor (TNF)-alpha for the treatment of inflammatory bowel disease (IBD). Since its introduction a decade ago infliximab (IFX) has revolutionised the management of complicated IBD, provided patient choice, enhanced quality of life and raised the bar for expected therapeutic outcomes from disease control to deep remission with complete mucosal healing and symptom resolution.[1]

Inflammatory bowel disease

The IBDs, Crohn's disease (CD) and ulcerative colitis (UC) are an internationally significant health problem characterised by life-long relapsing-remitting gastrointestinal inflammation. Although the aetiology is unknown, it is widely accepted that genetic and environmental factors combine to result in abnormal host recognition of luminal antigens and a sustained, pathological, mucosal inflammatory response.[2] Active disease is typically associated with the passage of bloody diarrhoea, abdominal pain and weight loss. Up to 40% of patients fail to respond to first-line therapy and as many as 20% of patients admitted to hospital with severe IBD require surgery.[3] The diagnosis of CD or UC is made on radiological, endoscopic and histological grounds with clear differences distinguishing the two. CD manifests as discontinuous chronic, transmural, granulomatous inflammation which may occur at any site within the gastrointestinal tract, although most commonly within the right colon and ileocaecum.[1,2] In contrast, UC is characterised by non-granulomatous inflammation, limited to the mucosa and submucosa, which extends continously from the rectum proximally for some distance.[1,2] With the exception of backwash ileitis, inflammation in UC is confined to the colon. Both UC and CD may be complicated by extraintestinal manifestations, the most frequent of which is articular disease.[1] In addition to extraintestinal manifestations, patients with IBD are at increased risk of gastrointestinal cancer, particularly of colorectal cancer in patients with long standing and extensive colonic disease. As a consequence of transmural inflammation and penetrating ulceration, CD may be complicated by the formation of fistulae, abscesses and intestinal strictures for which surgical intervention may be required.[4,5] Although the anatomical location of disease is relatively stable, the severity of the disease changes significantly over time[6] and while 60-70% of individuals with CD have non-stricturing, non-penetrating disease at diagnosis, more than 33% will develop stricturing or penetrating disease within 10 years.[6-8] Perianal fistulae may occur in greater than one fifth of patients.[9]

The prevalence of IBD in New Zealand

Studies have shown a dramatic rise in the incidence of IBD in NZ in the last 50 years,[10] with a particularly high incidence of the disease in the Canterbury region (CD 16.5/100 000; UC 7.6/100 000; 2004 data) which is likely to reflect the situation throughout NZ.[11] The prevalence rates of CD and UC in that region in mid 2005 were 155.2/100 000 and 145/100 000, respectively. The estimated incidence in the paediatric population in NZ in 2002-03 was 2.9/100 000; this rate was comparable to that seen in North America and the UK.[12] Furthermore, given the high rates of IBD seen amongst the second generation of Asian immigrants to other countries, we might expect to see an increase in the incidence of IBD in non-Caucasian populations in NZ.[13] There are currently approximately 10,000 people with IBD in NZ.

The economic and individual burden of IBD

IBD carries with it a significant resource burden, both direct through healthcare expenditure, and indirect. Recent research by Lion and colleagues estimates that in New Zealand, CD costs more than $58 million annually in healthcare expenditure, a significant proportion of which is associated with the treatment of fistulising disease (*unpublished data*). Indirect costs are harder to estimate. Studies have consistently shown significant reduction in quality of life for patients with IBD.[13-15] Furthermore, as disease onset is most common during young adult years[16], lost productivity applies not only to work, but also to educational and social activities resulting in a detrimental effect on long-term personal and professional achievement. Children with IBD not only have a more aggressive phenotype of IBD, but also live with the illness for longer with consequent negative medical, nutritional and psychological impacts.[10]

Treatment options in IBD

Drug treatment of both CD and UC has traditionally been delivered in a stepwise manner, with the least toxic therapies being used early during the course of disease and other more potent drugs added as required.[17] Guidelines from both the US and Europe recommend such an approach.[18-20] Corticosteroid preparations, which may be administered intravenously in high doses for severe disease, are useful for the induction of remission of active UC and CD, but have no role in maintenance therapy, have a low potential to heal inflammatory lesions[21], may be associated with adverse long-term outcomes in CD and have a significant adverse effect profile. Mesalazine drugs may be used for both induction of remission in mild-to-moderate disease, either alone or as combination therapy, and are also useful maintenance agents. The introduction of anti-TNF therapies has dramatically improved therapeutic capability in IBD. IFX (a chimeric monoclonal antibody to TNF) and adalimumab (a fully humanised monoclonal antibody to TNF) have proven effect for the induction and maintenance of remission in CD, while IFX is also an effective treatment in moderate-to-severe UC. The immunomodulators azathioprine (AZA), 6-mercaptopurine and methotrexate are effective in maintaining remission (methotrexate, CD only); however, their onset of action is usually too slow for them to have a role in induction therapy.[17]

Recent evidence suggests that the traditional step up algorithm (in the order mesalazine, corticosteroid, immunomodulator and biological) may not represent optimal therapy for CD. A recently explored approach to management in CD is based on the premise that biological agents, such as IFX, can heal mucosa and possibly alter the natural course of the disease.[17] 'Step down' therapy would use biologics to induce a rapid and sustained remission with the hope of reducing the need for future surgical intervention.[17] A recent randomised trial showed superior efficacy for early combined immunosuppression (IFX and AZA) compared with conventional therapy in steroid-naïve patients with recently diagnosed CD.[22] Another large randomised controlled trial, the SONIC trial, showed that steroid- and immunosuppressant-naïve patients with moderate-to-severe CD who received AZA monotherapy were less likely to have a corticosteroid-free remission than those receiving either IFX monotherapy or IFX plus AZA.[23]

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About Research Review

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Infliximab

IFX 100mg powder for injection was approved in New Zealand in 2000 for use in moderate-to-severe CD in adults and children >6 years of age, and in active UC in adults (≥18 years).[24] It is also approved for use in adults for rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis.

Pharmacological properties

IFX binds with high affinity to both the soluble and the transmembrane forms of TNF-alpha, and acts to antagonise the proinflammatory actions of TNF.[24] It has also been shown to cause down regulation of proinflammatory cytokines and to have pharmacological effects on several other biomarkers of CD.[25] Importantly, it appears that IFX acts without causing generalised suppression of systemic immune function.[26] It should be noted, however, that there are increasing numbers of reports of invasive infectious diseases developing following use of the agent.[27]

The pharmacokinetics of IFX are linear within the dosage range of 3-20 mg/kg and single IV infusions of 1, 3, 5, 10 or 20 mg/kg produced dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve.[24] Median C_{max} values at single doses of 3, 5 and 10 mg/kg were 77, 118 and 277 µg/mL, respectively.[24] The steady-state volume of distribution, mean residence time, clearance and elimination half-life are all independent of dose.[25] IFX exhibits a long elimination half-life (median 8–12 days) and is still detectable in plasma up to 12 weeks after the last dose; 8 weeks after a maintenance infusion ≈20% of patients had undetectable serum IFX concentrations.[24,25] Paediatric patients seem to exhibit a similar pharmacokinetic profile for IFX to that seen in adults.[28]

Indications in CD[24]

In adults, IFX is indicated for the treatment of moderate-to-severe CD for the reduction in signs and symptoms, induction and maintenance of clinical remission, induction of mucosal healing and improvement in quality of life in patients who have an inadequate response to conventional therapies. It is also indicated for the treatment of draining enterocutaneous fistulae.

In children and adolescents (6-17 years), IFX is indicated for the treatment of patients with moderate-to-severe, active CD who have not responded to a full and adequate course of conventional therapy, or who have medical contraindications to, or are intolerant to, such therapy.

Indications in UC[24]

In NZ, IFX is not approved for use in children and adolescents with UC. In adults with UC, IFX is indicated for reducing signs and symptoms, inducing and maintaining clinical remission, inducing mucosal healing, improving quality of life, reducing or discontinuing administration of corticosteroids, reducing UC-related hospitalisations and reducing the incidence of colectomy in patients with active UC who have had an inadequate response to conventional therapy.

Dosage and administration[24]

IFX is to be administered under the supervision of specialised physicians and all patients must be observed for at least 1 hour post infusion for side effects.

Moderate-to-severe CD in adults and children >6 years

As an induction regimen, 5 mg/kg given as a single IV infusion over a 2-hour period at 0, 2 and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. The dosage may be adjusted up to 10 mg/kg in patients exhibiting an incomplete response during maintenance therapy.

As an alternative, an initial 5 mg/kg IV infusion may be administered over a 2-hour period, followed by repeat infusions of 5 mg/kg when signs and symptoms of CD recur.

For paediatric patients not responding within 10 weeks of initial infusion, data does not support the use of extended therapy.

Fistulising CD

For the treatment of draining fistula(e) in CD, infuse 5 mg/kg IV over a 2-hour period, followed with additional 5 mg/kg doses administered at 2 and 6 weeks. Additional treatment with IFX should not be given if there is no response after 3 doses.

UC

5 mg/kg given as an IV infusion over a 2-hour period followed by additional 5 mg/kg infusions at 2 and 6 weeks, then every 8 weeks thereafter. The dose may be increased to 10 mg/kg in order to sustain clinical response and remission.

Readministration for CD

If signs and symptoms of disease recur, IFX can be readministered within 16 weeks following the last infusion.

Readministration for UC

Data supporting readministration, other than every 8 weeks, are not available.

Availability of infliximab in NZ

The availability of IFX in New Zealand has been variable since it first became available for CD and subsequently UC. As this treatment is provided in hospitals, access to it has been determined by each individual District Health Board (DHB). Tan et al presented a survey in 2007 showing that access to IFX for the treatment of IBD differed across New Zealand dramatically depending on which DHB one lived in (*unpublished data*). Such postcode prescribing is thought to be due to financial constraints imposed by individual DHBs and lack of specialist Gastroenterologists with an interest in IBD in some DHBs. At the time of writing, access to IFX has improved across New Zealand, but probably remains below that suggested by national and international guidelines.

Specialist commentary on current treatments

Clinical efficacy and safety of infliximab in the treatment of IBD

The efficacy of IFX in treatment-resistant moderate-to-severe CD was demonstrated in a pivotal study by Targan et al in 1997, in which 65% of patients exhibited a clinical response, and 33% experienced remission 4 weeks after receiving a single 5-20 mg/kg dose of IFX.[29] Several subsequent studies have shown similar findings, with IFX exhibiting efficacy for both the induction and maintenance of remission in moderate-to-severe CD.[30-33] Other studies have demonstrated the efficacy of IFX in adults with fistulising disease,[34-36] in paediatric patients[28,37,38] and in patients with UC.[39,40]

IFX is generally well tolerated, but potentially serious adverse events have been noted during treatment with anti-TNF-alpha therapy and include the recrudescence of tuberculosis and other serious infections, worsening of heart failure, demyelinating disease and malignancy (particularly lymphoma).[25] Two recent large cohort studies evaluating the long-term safety profile of IFX in IBD showed that serious adverse events occur at a rate of <13% and concluded that the agent is well tolerated and safe when recommended preventive measures are implemented.[41,42] A selection of key studies is discussed in more detail below.

Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial[30]

Authors: Hanauer SB et al

Summary: The multicentre, randomised controlled, double-blind ACCENT I trial involved 573 IFX-naïve adult patients with CD of ≥3 months duration and a CD Activity Index (CDAI) score of 220-400 points who received a single IV infusion of IFX 5 mg/kg. The trial examined the efficacy and safety of IFX as maintenance therapy in responders to the initial infusion. 335 patients (58%) exhibited a response to the infusion at week 2 (defined as a decrease in CDAI score of ≥70 points from baseline and a ≥25% reduction in the total score CDAI score). Responders were randomly assigned to receive one of three treatments: IV infusions of placebo (group I, n = 110), IFX 5 mg/kg at weeks 2 and 6, and every 8 weeks thereafter until week 46 (group II, n = 113), or IV infusions of IFX 5 mg/kg at weeks 2 and 6, followed by 10 mg/kg infusions 8 weekly (group III, n = 112). Corticosteroids were being taken by 52% of responders at week 2. At week 30, the proportion of week 2 responders still in clinical remission (CDAI <150 points) was significantly ($p<0.001$) higher among those receiving maintenance IFX (39%, group II; 45%, group III) compared with those receiving placebo (21%, group I). The odds ratio (OR) for remission at 30 weeks in groups II and III combined was 2.7 (95% CI 1.6-4.6). Similar findings were seen at week 54. There was no significant difference in the rate of clinical remission between groups II and III at either 30- or 54-week follow-up. Similar findings were seen with regard to clinical response. The median time to loss of response was significantly ($p<0.001$) less for the placebo group (19 weeks) compared with groups II and III (38 and >54 weeks, respectively). Serious adverse events were reported in 29%, 28% and 22% of groups I, II and III, respectively, during the 54-week study period. The proportion of patients who experienced a serious infection was similar among the three groups (3-4%).

Comment: Successful treatment of CD with IFX was first reported in 1995 in a small open-label study involving 10 patients, 8 of whom responded.[43] Two years later, the first randomised control trial of IFX for the treatment of CD was reported by Targan et al.[29] In that study, patients were treated with either placebo, or a single dose of IFX at either 5, 10 or 20 mg/kg. Although 33% of patients had achieved remission and 65% had responded to treatment after 4 weeks, the clinical response was not durable with nearly two thirds of patients relapsing by 12 weeks. No dose-response relationship was seen between the IFX groups. Subsequently, in an extension of the trial, Rutgeert's[31] demonstrated the potential benefit of maintenance therapy by randomising patients with clinical response at 8 weeks to receive either retreatment with IFX (10 mg/kg) or placebo 8 weekly for 4 doses. Although there was no significant difference in the median time to loss of response due to the size of the study, clinical response was significantly more likely in patients retreated with IFX than in those receiving placebo (72% and 44% respectively), setting the scene for further investigation of IFX as a maintenance agent in CD. Furthermore, in the initial study by Targan, 29 patients who failed to respond to an initial infusion received a second dose which resulted in 34% of these patients achieving a clinical response (17% remission), demonstrating that repeat dosing in non-responders improved overall remission rates.[29] The ACCENT 1 trial marks a watershed for the treatment of CD in that the investigators not only replicated elements of each of the preceding trails, but also, and conclusively, demonstrated the benefit of maintenance IFX therapy for the prevention of disease relapse in a group of patients broadly representative of the CD population. Specifically, 3 dose induction at 0, 2 and 6 weeks was significantly better than single dose induction therapy at both 10 and 14 weeks, maintenance therapy doubled the number of patients in clinical remission at week 54 when compared with placebo, and in line with Targan's study, no significant benefit was achieved with high dose IFX. Consequently, the protocol used in ACCENT 1 persists as the standard regime for the induction and maintenance of remission of CD today.

Infliximab maintenance therapy for fistulizing Crohn's disease[34]

Authors: Sands BE et al

Summary: The multicentre, randomised controlled, double-blind ACCENT II trial involved 306 adult patients with CD who had had single or multiple draining fistulas for ≥3 months and who received an IV infusion of IFX 5 mg/kg at weeks 0, 2 and 6. The trial investigated the efficacy and safety of maintenance IFX in a total of 195 patients who had exhibited a response to the agent, defined as a reduction of ≥50% from baseline in the number of draining fistulas at 10 and 14 weeks. Responders were randomly assigned to receive either IFX 5 mg/kg (n = 96) or placebo (n = 99) every 8 weeks, up to week 46. Patients were followed until week 54 and were assessed for loss of response, defined as recrudescence of fistulas, the need for a change or addition to CD therapy for persistent or worsening luminal disease, the need for surgical intervention, or the discontinuation of study medication due to a perceived lack of efficacy. The time to loss of response was significantly ($p < 0.001$) longer for IFX recipients than placebo recipients (median >40 weeks vs 14 weeks). Furthermore, at week 54, significantly ($p < 0.01$) more IFX recipients exhibited a complete response (absence of draining fistulas) to therapy than placebo recipients (36% vs 19%). Patients with fistulas appeared to tolerate IFX maintenance therapy well.

Comment: The ability to heal and prevent recrudescence of fistulising disease in a durable manner represents a major advance in the management of Crohn's Disease. While the use of IFX to heal fistulising CD was established by Present et al in 1999 (68% response and 55% closure of all fistulas compared with 26% for placebo), the median time to relapse was only 3 months.[35] In the ACCENT II trial, clinical response was comparable to the previous study, however, use of maintenance IFX therapy sustained complete clinical response up to 1 year in 36% of cases compared with 19% of controls and prolonged the median time to loss of response from 14 to 40 weeks. Patients without response to the initial induction regimen were also randomised in the same way as responders. Importantly, those without a response to induction therapy showed no additional benefit to maintenance IFX. Furthermore, of those who lost response following initial successful induction therapy, escalation of therapy to IFX 5 mg/kg (for those receiving placebo) or IFX 10 mg/kg for those receiving 5 mg/kg maintenance, re-established response in 61% and 57% of subjects respectively, indicating the benefit of escalation therapy in this group of patients. The development of fistulising disease is feared by both patient and physician alike. Current best practice recommends aggressive medical therapy with biological agents in combination with surgical investigation and treatment in order to optimise clinical success, and minimise patient suffering and tissue damage due to inadequately controlled disease.

Infliximab, azathioprine, or combination therapy for Crohn's disease[23]

Authors: Colombel JF et al

Summary: The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) was a multicentre, randomised, double-blind trial in adult patients with moderate-to-severe CD of ≥6 weeks duration and a CDAI score of 220-450 points. A total of 508 patients were randomised to either IV infusions of IFX 5 mg/kg plus daily oral placebo (n = 169); placebo infusions plus oral AZA 2.5 mg/kg/day (n = 170); or combination therapy with IFX and AZA (n = 169). Infusions were administered at weeks 0, 2 and 6, and then every 8 weeks. At 30-weeks' follow-up, patients were given the option to continue to receive their assigned blinded therapy in a 20-week extension trial. The primary endpoint, corticosteroid-free remission at week 26, was achieved by significantly more patients in the combination therapy group (56.8%; 96/169) when compared with either IFX ($p = 0.02$) or AZA ($p < 0.001$) monotherapy, and significantly more likely among those receiving IFX monotherapy (44.4%; 75/169) when compared with AZA monotherapy (30%; 51/170; $p = 0.006$). A similar trend was found at week 50. The incidence of adverse events, including serious infections, was similar among the three groups.

Comment: The SONIC trial represents the culmination of a decade of experience with IFX therapy and in particular a move towards early use of immunosuppressive agents or so called top down therapy. The SONIC trial not only provides robust evidence that combination therapy with IFX and AZA is better than AZA monotherapy, but also demonstrates the superior outcomes achieved with IFX monotherapy when compared with AZA treatment alone. Results remained significant at 50 weeks even when patients who did not join the voluntary trial extension were considered to have loss of response. In addition to symptomatic improvement, mucosal healing was achieved significantly more often in the combination therapy group (43.9%, $p \leq 0.06$) compared with those receiving IFX or AZA monotherapy (30.1% and 16.5%, respectively). Taken together with results from a previous investigation of top down vs step up therapy[22], it would appear that early combination therapy provides the optimal therapeutic response with IFX use. Several concerns exist however. Firstly in relation to the consequences of long-term exposure to combination immunosuppressives in a predominantly young adult population (in particular the risk of Hepato-splenic T cell lymphoma in young males), and secondly regarding the economic cost of therapy with biologics. In the absence of clear data in either regard, one strategy that gastroenterologists might employ is stratification of patients according to risk of developing complicated CD based on disease characteristics at presentation, extent, and the presence of serological markers. In patients commenced on combination therapy, cessation of one drug or the other may be considered at a later time, however, evidence to support decision making in this situation is limited.

Infliximab for induction and maintenance therapy for ulcerative colitis[39]

Authors: Rutgeerts P et al

Summary: The efficacy of IFX for the induction and maintenance of remission in adult patients with moderate-to-severe active UC was examined in the multicentre, randomised controlled, double-blind Active Ulcerative Colitis 1 and 2 trials (ACT 1 and 2). Each trial involved 364 patients who were randomised to receive IFX 5 or 10 mg/kg, or placebo at weeks 0, 2 and 6 and then every 8 weeks to week 46 (ACT 1, 5ASA disallowed) or week 22 (ACT 2, 5ASA allowed). In both studies, there were between 120 and 123 patients in each of the three treatment groups. In ACT 1, a clinical response (defined as a ≥3 point and a ≥30% reduction from baseline in Mayo score, along with a decrease in the subscore for rectal bleeding of ≥1 point, or an absolute rectal-bleeding subscore of 0 or 1) was achieved at week 8 by significantly ($p < 0.001$) more IFX 5 mg/kg and IFX 10 mg/kg recipients than placebo recipients (69% and 61% vs 37%, respectively). In ACT 2, the percentages at week 8 were 64% and 69% vs 29%, respectively ($p < 0.001$ for both comparisons with placebo). In both studies, clinical response at week 30 was significantly ($p \leq 0.002$) more likely in IFX recipients than placebo recipients. In ACT 1, this trend was evident at week 54, with significantly ($p < 0.001$) more IFX 5 mg/kg recipients and IFX 10 mg/kg recipients exhibiting a clinical response compared with placebo recipients (45% and 44% vs 24%, respectively).

Comment: Despite an earlier randomised control trial which failed to demonstrate a significant benefit from IFX in patients with moderate glucocorticoid resistant UC[44], both ACT 1 and ACT 2 and subsequent studies have confirmed the value of IFX for the treatment of moderate-to-severe UC.[40] As with the earlier study, patients recruited to ACT 1 and ACT 2 had demonstrated resistance or intolerance to glucocorticoid therapy, however, as less than a third of patients had steroid refractory disease and disease was limited to the left colon in the majority of patients, the ACT study cohorts are distinguishable from cohorts of severe or fulminant colitis refractory to corticosteroids who may benefit from IFX rescue therapy.[40, 45] Nevertheless, ACT1 and ACT2 establish the effectiveness of IFX therapy for both induction of remission and subsequent maintenance therapy for patients with less severe disease, with two thirds of patients demonstrating clinical response at 8 weeks and one third clinical remission at the same time point. By week 30 approximately half of patients in the treatment groups showed persistent response compared with 30% in the placebo arm and at week 54, patients who received IFX were approximately twice as likely to have persistent response compared with those in the placebo arm. Remarkably, reported rates of mucosal healing were higher than those of clinical remission suggesting that the threshold for attributing mucosal healing in these studies was too low. Nevertheless, taken together, the evidence indicates that IFX is effective both as an induction agent and for the maintenance of remission in UC.[46]

Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study[41]

Authors: Fidder H et al

Summary: This recent Belgian, single-centre, retrospective cohort study investigated the long-term safety of IFX in patients with IBD. The study authors assessed the medical records of 734 patients (6% children or adolescents) with IBD who had received IV IFX 5-10 mg/kg (median of 6 infusions; 92% of patients received >1 infusion) and 666 controls who had not received the agent; median follow-up 58 months and 144 months, respectively. During the follow-up period, serious adverse events occurred in 13% (93/734) of IFX recipients and 19% (126/666) of controls. Furthermore, there were no differences between the groups in the rates of malignancy, mortality or infection. Two IFX recipients developed tuberculosis during treatment with the agent. The only independent risk factor for developing infection was concomitant treatment with corticosteroids (OR 2.69; 95% CI 1.18-6.12). Skin eruptions were the most commonly observed systemic side effect, occurring in 20% of IFX recipients. The authors concluded that, in their cohort, long-term IFX therapy had a good overall safety profile.

Comment: Fidder presents long-term, post-marketing surveillance data on 734 unselected consecutive patients with IBD treated with IFX in a single centre since 1994. It is the largest study of its kind. It is notable therefore that no difference in risk of death, severe infection or malignancy was found between the two retrospective cohorts, indicating that the use of IFX is no worse than conventional therapy in this regard. While patients may be reassured that IFX therapy does not expose them to greater risk of harm than conventional therapy, physicians will appreciate that use of biological agents is associated with a unique adverse effect profile. In particular increased susceptibility to fungal infection and intracellular pathogens including *Mycobacterium tuberculosis*, risk of acute and delayed type hypersensitivity to IFX administration, and more recently concern over an apparent association with the rare, but invariably fatal hepato-splenic T cell lymphoma (HSTL). Acute infusion reactions occurred in 17% of cases in Fidder's study, but with careful management discontinuation of infusion was required in only a minority of cases. Cumulative experience indicates that infusion reactions are more likely to occur with episodic treatment. Co-prescription of immunomodulators and/or corticosteroids, and the use of induction schedules and maintenance infusions all minimise the risk of infusion reactions.[30,34,41] Serious adverse events occurred in 13% of patients in the IFX group. Of 12 deaths among 743 treated with IFX, only one was considered to be directly related to IFX. The only predictive factor of death was old age and the median age of death did not differ significantly between the 2 groups. Notably, although patients in the IFX group were younger and more likely to have received immunomodulator therapy, concomitant treatment with immunomodulators was not predictive of infectious complications, either in this study or previously.[23] Furthermore, and in line with previous studies, risk of infection was significantly increased by concomitant corticosteroid therapy.[47] Reactivation of tuberculosis (TB) is a well documented complication or IFX therapy[23,39,41] In Fidder's study, 16 patients had evidence of previous TB infection and received anti-TB chemoprophylaxis, yet none developed TB during follow-up confirming the safety of this approach. No increased risk of malignancy was observed among those patients receiving IFX. There were no cases of HSTL. Concomitant use of immunomodulator therapy was not associated with increased risk of malignancy on univariate or multivariate analysis, however, longer disease duration and older age were predictive for malignancy in both groups. Resource considerations aside, concerns about drug safety, and in particular, safety in the context of long-term therapy in combination with immunosuppressive agents, presents the single greatest concern for physicians prescribing anti-TNF biological agents. Fidder's study goes far in assuaging these concerns; however, biological-specific risks endure and require mindful pre-screening, counselling, surveillance and follow-up as part of usual specialist IBD care.

CONCLUSION

IFX has represented a major advance in the medical therapy for IBD. It is the first effective biological agent for IBD and has been used successfully around the world to manage moderate-to-severe CD, fistulising CD, paediatric CD and moderate-to-severe UC. As we have learned more about this agent, we have also seen the potential advantages of using it early in the course of CD, particularly in those patients with poor prognostic signs. While it is not without adverse effects, these have been better described for this agent than for other biologicals in clinical trials and post-marketing surveillance. This agent plays a crucial role in the modern management of IBD and it is important that access to it is equal across New Zealand, in line with local and international guidelines.

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Treatment decisions based on these data are the full responsibility of the prescribing physician.