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REVIEW

Cause for controversy? Infliximab in the treatment of ulcerative colitis: an update

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Abstract: Infliximab is a monoclonal antibody against tumor necrosis factor (TNF) which has become an established therapy for Crohn's disease over the last 10 years. Given the similarities between Crohn's disease and ulcerative colitis (UC), it is no surprise that gastroenterologists have used infliximab in patients with UC who have failed other therapies. Although the initial controlled trials with infliximab in steroid-refractory disease were unimpressive, subsequent controlled trials have demonstrated the efficacy of infliximab in both moderate to severe disease, and as rescue-therapy to avoid colectomy. The long-term remission rates, colectomy-sparing effects, and the impact of concomitant immunomodulator therapy, remain to be determined in these patients. Whether infliximab is a superior strategy to cyclosporine in patients with steroid-refractory disease is controversial. This review examines the data on the efficacy and safety of infliximab as an induction and maintenance agent for UC.

Keywords: ulcerative colitis, infliximab, biologics

Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disease of the colon. The characteristic phenotype typically involves only the colon, though extra-intestinal manifestations may occur, affecting the joints, liver, eyes and skin. UC shares the umbrella term "inflammatory bowel disease" (IBD) with Crohn's disease, though their phenotypes differ substantially, particularly as Crohn's disease can affect any part of the gastrointestinal tract. The prevalence of UC varies worldwide, though retrospective studies suggest that it is more common in Northern Europe, the UK, and North America.[1,2] However, there are reports of increasing incidence and prevalence in south and central Europe, Asia, Africa, and Latin America.[1,3] In the US, the prevalence among adults ranges from 37 to 246 per 100,000 population.[4] Similarly, European prevalence rates vary widely, ranging from 21 to 243 per 100,000 population.[1]

Though UC can occur at any age, it typically presents in youth, between 15 and 35 years, with a second peak incidence in the 55- to 65-year-old age group.[5] The typical symptoms of UC include rectal bleeding, abdominal pain, diarrhea, weight loss, and growth failure. Less common symptoms include joint pain, dry eyes and rashes. These symptoms can be exacerbated by antibiotic use, cessation of smoking, use of NSAIDs, and psychological stress.

The etiology of UC is unclear, but our current understanding is that an environmental trigger in susceptible individuals leads to dysregulated inflammation and tissue damage.[6]

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The environmental trigger has yet to be defined, and there does not appear to be a single dominant pathogenic gene that increases susceptibility to UC. Genome-wide association studies have implicated susceptibility regions on at least 12 chromosomes to date.[7]

Once an inflammatory cascade has been elicited, both macrophages and T-lymphocytes play a role in propagating tissue damage in the intestinal mucosa. T cell activation in UC has historically appeared to be initiated with a predominantly T-helper-2 (Th2) cytokine profile, maintained by interleukin-12 (IL-12) activity.[7] This leads to inflammatory cytokine release, including IL-5 and IL-13, and appears to indirectly stimulate macrophages to release tumor necrosis factor (TNF) and IL-1 and IL-6, which further drive the inflammatory cascade. This can be contrasted to Crohn's disease, which has a cytokine profile more associated with T-helper-1 (Th1) cells.

Recently, the emergence of a more complex framework of T-helper cell activity has led to the recognition of a role for T-helper-17 (Th17) cells, derived from a lineage separate to that of Th1 and Th2 cells. Activation and maintenance of these cells, driven by IL-23 (of the IL-12 family) leads to heightened IL-17 production.[8] This IL-23/IL-17 axis of inflammation appears to be an important component in intestinal inflammation in IBD;[9] animal models of colitis, and human studies of patients with active UC, have reported a higher proportion of TH17-producing IL-17 cells in the inflamed mucosa.[10–12] Of note, inhibition of TNF significantly decreased expression of IL-23 and IL-17 in an animal model of colitis, suggesting TNF remains an intricate component of the IL-17/IL-23 pathway also.[13]

The traditional therapeutic strategies for UC target these inflammatory pathways to induce a clinical response and/or maintain disease remission.[14] Drugs that release 5-aminosalicylic acid (5-ASA) (mesalazine, sulphasalazine, olsalazine, balsalazide) have topical anti-inflammatory effects in the colon, and can be administered orally or rectally. They have proven efficacy in both the induction and maintenance of remission of UC. In patients with more severe disease, steroids (prednisone, hydrocortisone) or cyclosporine have been used to induce remission of disease. Immunomodulators, such as azathioprine or 6-mercaptopurine (6-MP), have typically been used to maintain the remission induced by steroids or cyclosporine, or in patients who are intolerant of 5-ASAs. Occasionally, patients with severe UC fail medical therapy, and need a colectomy.

The agents discussed above exert their anti-inflammatory action by broad, nonspecific effects on immune cell function, with often poorly understood mechanisms of action. The development of infliximab led to the emergence of cytokine-specific agents with a more defined target, in this case TNF and TNF-bearing cells.

Rationale for the use of anti-tumor necrosis factor (anti-TNF) in UC

TNF was first described in 1975[15] and named for its ability to lyse tumors *in vitro* and in mouse models. It is a cytokine that is initially membrane-bound (mTNF) on its source cells, but released as soluble TNF (sTNF) after enzymatic cleavage by TNF converting enzyme (TACE). TNF is produced by activated macrophages and T cells in areas of inflammation, and plays a role in the pathogenesis of UC. As a ligand it has a number of biological effects in inflammatory states:[16]

- neutrophil migration to the inflamed colon
- activation of $CD4^+$ lymphocytes
- activation of matrix metalloproteinases
- weakening of cellular tight junctions
- inhibition of apoptosis of T-cells

Increased concentrations of TNF have been reported in the blood, colonic tissue and stool of patients with UC.[17–19] Upregulation of TNF converting enzyme (TACE) has also been demonstrated in UC, which is important for conversion of mTNF to sTNF.[20] TNF has thus a critical role in localized and systemic inflammatory reactions, and inhibition of TNF activity would be expected to have anti-inflammatory benefits.

Pharmacology of infliximab

Development

Anti-TNF antibodies were first manufactured in the 1990s[21] and infliximab (Remicade®; Centocor, Malvern, PA, USA became the first commercially available form. It is a chimeric) antibody to TNF (human IgG1 coupled to the variable regions of mouse anti-TNF), with a high affinity to the soluble and trans-membrane forms of TNF, thus binding both forms of this cytokine.[22] Infliximab was approved for use by the Food and Drug Administration (FDA) in moderate to severe fistulizing Crohn's disease in October 1998,[23] and a year later in rheumatoid arthritis (RA) (November 1999).[24] Its license has since been extended for use in ankylosing spondylitis, plaque psoriasis and psoriatic arthropathy.[25] Off-label uses include Behçet's syndrome, uveitis, erythrodermic psoriasis, and pyoderma gangrenosum. Finally, in October 2006, infliximab was the first anti-TNF antibody to be licensed for use in the treatment of moderate to severe UC.[26] The European Medicines Agency (EMEA) approved infliximab for the treatment of severe or fistulizing Crohn's disease in August 1999,

and for RA in June 2000.[27] Licensure for use of infliximab in severe UC occurred in October 2006.[28]

Pharmacokinetics

Infliximab binds specifically to human TNF-α with an association constant of 10^{10}/M.[29] After intravenous (iv) infusion of 5 mg/kg, the C_{max} is 118 μg/mL, and infliximab is cleared from the circulation at a rate of 10 mL/h. By week 12 after infusion, infliximab levels are near undetectable (median concentration <0.1 μg/mL) with the 5 mg/kg dose but a dose of 10 mg/kg iv maintained therapeutic concentrations for a longer period. The volume of distribution of infliximab is 3 to 6 L, and serum levels decline slowly in a linear manner, leading to an elimination half-life of 7 to 12 days.[25,30]

Repeated doses of infliximab do not appear to result in accumulation; in one study in which Crohn's patients were receiving 10 mg/kg infusions and had blood taken prior to each infusion, median serum infliximab concentrations were 7.9, 10.0, 8.1, and 8.0 g/mL at weeks 20, 28, 36 and 44, respectively.[31] Recommended dosing for UC reflects that for Crohn's disease; 5 mg/kg iv over 2 hours at 0, 2 and 6 weeks, followed by 5 mg/kg iv maintenance therapy every 8 weeks thereafter. If patients prove refractory, dose may be increased to 10 mg/kg at the regimen above, or 5 mg/kg doses may be given as maintenance at 6-weekly intervals, a strategy that has been used in Crohn's disease to overcome antibodies to infliximab (ATIs).[32,33]

Mechanisms of action

At a molecular level, infliximab was initially thought simply to bind to soluble TNF and thus neutralize its pro-inflammatory effects. Subsequent experiments in humans and *in vitro* have demonstrated that anti-TNF antibodies can:

- induce apoptosis in monocytes and lymphocytes by binding membrane-bound TNF[34,35]
- decrease *in vitro* production of TNF and IFN-γ by intestinal/peripheral blood T cells[36]
- disrupt CD40/CD40L pathways in peripheral blood lymphocytes[37]
- inhibit granulocyte-macrophage colony stimulating factor production by T-lymphocytes[38]
- restore the gut barrier in patients with Crohn's disease[39]
- inhibit integrin expression on the endothelium[40]

Technetium-labeled infliximab studies have demonstrated no or minimal uptake of infliximab in the intestine up to 20 hours after infusion, suggesting that its initial main location of action is in the blood stream.[41] Complementary to this, many molecular events begin early after infusion of infliximab; C-reactive protein and IL-1β levels fall within hours, and whole blood levels of TNF drop significantly within 24 hours of infusion.[42]

Recent *in vitro* data have demonstrated that infliximab neutralizes both membrane and soluble TNF, inhibits IL-1β release from monocytes, and induces cytotoxicity and apoptosis.[43] TNF neutralization *per se* may not be the main mechanism of action in IBD, as the recombinant human soluble TNF receptor etanercept was not efficacious in Crohn's disease in a clinical trial,[44] despite the fact that it binds to both mTNF and sTNF, and induces apoptosis.[45] Thus, the mechanisms through which infliximab mediates its anti-inflammatory effects in UC are multi-factorial. It has been proposed that reverse signaling through the TNF receptor may play a role.[46] Infliximab can bind mTNF, and mTNF can activate NFkB pathways in leukocytes.[47] Almost all these data comes from animal models, or samples from patients with Crohn's disease, although it is assumed the mechanisms are relevant to UC.

Clinical trials of infliximab in UC

Evidence for the efficacy of infliximab in UC comes from a series of open-label studies, randomized controlled trials (RCTs), and meta-analyses. The outcomes seen with infliximab in these trials can be considered to be typical patient populations seen in clinical practice; moderate to severe UC, steroid-refractory UC, and cyclosporine-refractory UC. Cyclosporine is also a valid therapy in some of these cohorts, and will be discussed below (Alternatives to infliximab).

Evidence from randomized controlled trials

Table 1 lists randomized trials in which response to infliximab is assessed with various endpoints such as clinical response, remission and colectomy rates. In patients with severe, steroid-refractory UC, the initial small trials demonstrated modest efficacy after single infusions when early clinical response was determined. The first published trial by Sands et al[48] in 2001 randomized 11 patients with steroid refractory UC to a single infliximab infusion or placebo, and noted a 50% (4/8) clinical response rate with infliximab at a week 2 evaluation (a further patient in the 20 mg/kg arm went into clinical remission by week 6). Subsequent studies by Probert et al[49] and Jarnerot et al[50] also enrolled patients with steroid-refractory disease. Probert et al failed to show any significant difference between placebo and 2 infusions of infliximab 5 mg/kg in endoscopic improvement or clinical remission. However, Jarnerot et al demonstrated in patients

Table 1 Data from randomized trials investigating response and remission rates for infliximab in patients with ulcerative colitis

Author	Year	N	Population	Clinical response (%)[a] within 8 weeks	Clinical remission (%)[a] within 8 weeks	Colectomy	Median follow-up
Sandborn et al[55,b]	2009	728	M-S and SR	n/a	n/a	46/484 (10%)	54 weeks
Rutgeerts et al[54] (ACT 1)	2005	364	M-S and SR	159/243 (65%)	86/243 (35%)		54 weeks
Rutgeerts et al[54] (ACT 2)	2005	364	M-S and SR	161/241 (67%)	74/241 (31%)		30 weeks
Jarnerot et al[50]	2005	45	SR	n/a	n/a	07/24 (29%)	6 months
Probert et al[49]	2003	43	SR	13/23 (57%)[c]	09/23 (39%)	0/23 (0%)	2 months
Sands et al[48]	2001	11	SR	5/8 (63%)[d]	2/8 (25%)	3/8 (37.5%)	3 months
Armuzzi et al[52]	2004	20	M-S	10/10 (100%)	10/10 (100%)	0/10 (0%)	9.7 months
Ochsenkuhn et al[53]	2004	13	M-S	05/06 (83%)	03/06 (50%)	0/6 (0%)	3 months

[a]Note definitions of clinical response and remission varied between groups.
[b]These patients represent 728 patients evaluated in ACT 1 and ACT 2.[54]
[c]These data represent endoscopic evidence of improvement, not clinical response.
[d]4/8(50%) patients achieved clinical response at week 2 evaluation; one further patient achieved clinical remission at week 6.
Abbreviations: M-S, moderate to severe ulcerative colitis; SR, steroid refractory.

with moderate and severe steroid-refractory UC that only 7/24 (29%) patients who received a single infliximab infusion underwent colectomy within 90 days (and indeed 6 months), compared with 14/21 (67%) who received placebo. The superiority of infliximab was only statistically significant in patients with moderate to severe disease (by Seo score), not in those with more severe disease on the fulminant colitis score, although the study was not powered to detect differences between these groups. At 2 years follow-up, the colectomy rate in patients who received infliximab had increased to 46%.[51] These studies positioned infliximab as a therapeutic option for patients with steroid-refractory disease.

Initial controlled trials[52,53] of patients who had moderate to severe disease only reported superior clinical response rates to those seen in steroid-refractory populations. These trials reported high response rates (100%, 83% respectively), but follow-up was short (9.7, 3 months, respectively). The ACT 1 and ACT 2 trials[54] each randomized 364 patients with moderate to severe UC who were failing conventional therapy(but did not require admission) to either placebo, or induction/maintenance infliximab 5 mg/kg or 10 mg/kg. Eligible patients had moderate to severe UC despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine in both ACT 1 and ACT 2 – ACT 2 also required that the patient failed 5-ASA therapy. In ACT 1, both doses of infliximab (5 mg/kg and 10 mg/kg) resulted in a statistically significant clinical response at week 8 (68.4% and 61.5% respectively, $P < 0.01$, compared to a placebo response of 37.2%). This was similar in ACT 2, with clinical response at week 8 of 64.5% in the infliximab 5 mg/kg group and 69.2% in the infliximab 10 mg/kg group, compared to a 29.3% response rate in the placebo group ($P < 0.001$). Clinical remission rates in the infliximab arms at week 8 ranged from 27.5% to 38.8% across both studies compared to placebo-induced remission rates of 14.9% (ACT 1) and 5.7% (ACT 2). Mucosal healing and steroid-free remission rates were also superior in the infliximab arms of these studies. Colectomy rates in patients in ACT 1 and ACT 2 were reported in a follow-up study by Sandborn et al.[55] The cumulative colectomy rate at 54 weeks was 10% in patients treated with infliximab, compared with 17% in those treated with placebo. These colectomy rates were not unexpected given the enrolled patients had moderate to severe disease, although there was incomplete colectomy follow-up data in 13% of the enrolled patients.

The ACT 1 and ACT 2 studies were well-designed, large studies, with comprehensive assessment of clinical and secondary endpoints. They provide important data to support the use of infliximab in patients with moderate to severe UC who have failed other therapies such as steroids, immunomodulators and mesalamine. However, infliximab is not a panacea for all; the proportion of patients who started the study on steroids, and were able to come off and remain in remission, was low (20%). This is comparable to the results in Crohn's disease with other anti-TNFs.[56]

Uncontrolled studies

A number of open label (and mostly retrospective) studies have been performed within the past 8 years, and though many have added weight to the above findings, some reports have been conflicting (see Table 2). Initial studies[57–62] mainly involved patients with steroid-refractory UC, and reported

response rates of 50% to 100%, and early remission rates of 20% to 100%. Colectomy rates varied greatly, ranging from 0% to 63%, though differences in duration of follow-up, and patient populations included, can explain these differences.

Larger cohorts of patients were reported in studies involving patients who were both steroid-refractory and steroid-dependent.[63–65] Response rates ranged from 67% to 100%, with early remission rates of 40% to 66%, somewhat similar to smaller studies of steroid-refractory UC. Again, colectomy rates differed, ranging from 11% to 60% with equally differing duration follow-up. A review of the uncontrolled studies with higher cumulative colectomy rates appear to include patients with more severe disease; criteria such as "severely ill" (Aratari)[62] and "candidate for colectomy" (Yamamoto-Furusho)[61] were used to select patients for infliximab in these studies.

As infliximab use became more common for severe UC, one clinical question that arose was its efficacy in patients with severe UC who had failed cyclosporine. Two small uncontrolled studies have addressed this issue.[66,67] Though numbers were small, response rates of 60% and 81% were achieved, with early remission rates of 40% and 77%, respectively. Considering these were patients who were likely to require colectomy soon, a colectomy rate of 40% and 38% in each study is lower than might be expected (follow-up 7.8 and 6.5 months respectively). The point to note in this scenario is the high rate of infectious complications in patients in these studies who have been treated with multiple immunosuppressants.[66]

Meta-analyses

Reflecting these findings, a meta-analysis by Gisbert et al[68] combined 34 studies (896 patients) of patients with severe acute UC and found response and remission rates of 68% and 40%, respectively, in the short term (median = 2.3 weeks), whereas in the long term (8.9 months) response and remission were found to be 53% and 39% respectively – all showed advantage of infliximab over placebo ($P < 0.001$) in all endpoints. Rahimi et al[69] in 2007 published data combining the results of 4 studies which showed a statistically significant summary odds ratio (OR) for clinical remission of 3.24 with a 95% confidence interval (CI) of 1.6 to 6.57. The summary OR for clinical response in 3 studies was 3.93 with a 95% CI of 2.84 to 5.45, again significant. Overall, infliximab was found to be effective in inducing response and remission in patients with UC when administered with corticosteroids. Finally, Lawson et al[70] performed a Cochrane database review of randomized trials in which infliximab was used to treat UC refractory to conventional therapies. Seven such trials were selected, and infliximab was noted to be more effective than placebo in producing clinical remission (relative risk [RR] 3.22, 95% CI 2.18 to 4.76), inducing endoscopic remission (RR 1.88, 95% CI 1.54 to 2.28) and in inducing clinical response (RR 1.99, 95% CI 1.65 to 2.41) at 8 weeks.

Table 2 Data from open label studies investigating the effect of infliximab in patients with ulcerative colitis

Author	Year	N	Population	Clinical response (%)[a] within 8 weeks	Clinical remission (%)[a] within 8 weeks	Colectomy	Median follow-up
Gonzalez-Lama et al[64]	2008	47	M-S and SR	47/47 (100%)	31/47 (66%)	05/47 (11%)	8.2 months
Willert et al[65]	2008	15	M-S and SR	13/15 (87%)	06/15 (40%)	09/15 (60%)	26 months
Su et al[63]	2002	27	M-S and SR	18/27 (67%)	12/27 (44%)	05/27 (19%)	4 months
Aratari et al[62]	2008	11	SR	11/11 (100%)		02/11 (18%)	24 months
Yamamoto-Furusho et al[61]	2008	10	SR	08/10 (80%)	02/10 (20%)	08/10 (80%)	12 months
Kohn et al[60]	2004	13	SR	10/13 (77%)	10/13 (77%)	03/13 (23%)	25.6 months
Actis et al[59]	2002	8	SR	04/08 (50%)	04/08 (50%)	05/08 (63%)	7 months
Kaser et al[57]	2001	6	SR	06/06 (100%)	04/06 (67%)	00/06 (0%)	5.5 months
Chey et al[58]	2001	8	SR	08/08 (100%)	08/08 (100%)	00/08 (0%)	2.3 months
Jakobovits et al[123]	2007	30	SR and CR		05/30 (17%)	16/30 (53%)	13 months
Bermejo et al[124]	2004	7	M-S and SR and CR	06/07 (86%)	06/07 (86%)	00/07 (0%)	6 months
Gornet et al[125]	2003	28	M-S and SR and CR	16/18 (89%)	09/18 (50%)		10 months
Manosa et al[67]	2009	16	CR	13/16 (81%)	10/13 (77%)	06/16 (38%)	6.5 months
Maser et al[66]	2008	10	CR	06/10 (60%)	04/10 (40%)	04/10 (40%)	7.8 months

Note: [a]Definitions of clinical response and remission varied between groups.
Abbreviations: CR, cyclosporine refractory; M-S, moderate to severe ulcerative colitis; SR, steroid refractory.

Safety of infliximab

The safety profile of infliximab has been established from a combination of case reports, postmarketing surveillance, and case-control studies, predominantly in patients with Crohn's disease, but also from the clinical trials of UC. The most common adverse events reported relate to transient infusion reaction, but more serious events such as infections and cancer have been described. It should be noted that most of the safety data come from studies on Crohn's disease and RA, in which concomitant immunosuppressives are used with infliximab, such as azathioprine, 6-MP or methotrexate. This can make it difficult to interpret which agent is contributing to adverse events.

Infusion reactions

Infusion reactions are the most common adverse event of the drug, and can manifest rarely as a true allergic reaction, or more commonly as non-specific mild infusion reactions that are classified as anaphylactoid (nonallergic), non-IgE mediated reactions.[71] Overall infusion reactions occurred in 10% and 18% of patients on infliximab in 2 studies.[72,73] Episodic therapy (episodic therapy involves giving infliximab as required, rather than regular maintenance infusions) has been associated with a higher risk of infusion reactions than regular maintenance therapy, presumably due to antibody formation between infusions.[72]

In ACT 1,[54] infusion reactions occurred in 13 patients (10.7%) in the placebo group, 12 (9.9%) of the 5 mg/kg infliximab group, and 15 (12.3%) of the 10 mg/kg infliximab group (no significant difference between infliximab and placebo). Similar numbers of events between placebo and infliximab groups also occurred in ACT 2.

Infections

Because TNF is involved in the immune system's response to infection, there were initial concerns and case reports that infliximab could increase susceptibility to serious infections. The large infliximab registry reported by Lichenstein et al[74] the TREAT registry, prospectively enrolled 6290 Crohn's patients, 3179 of whom were on infliximab (5519 patient-years). Mean follow-up was of 1.9 years. Serious infections occurred more commonly in infliximab-treated patients than placebo (1.37 per 100 patient-years vs 0.65 per 100 patient-years). However, infliximab patients were inherently sicker, with a more severe disease course, had more hospitalizations, and more surgeries. Thus, after multivariate analysis logistic regression, infliximab was not seen to be an independent risk factor of serious infection (odds ratio [OR] 0.99). Rather, prednisolone use was noted to be an independent risk factor for serious infection (OR 2.21). One meta-analysis[75] of randomized clinical trials of infliximab and adalimumab that included 3493 patients with RA revealed a pooled OR for serious infection of 2.0 (patients taking anti-TNF group were twice as likely to develop serious infection compared to patients who were not on anti-TNF). Of the 126 serious infections, 12 were granulomatous (10 cases of tuberculosis [TB], 1 histoplasmosis and 1 coccidiomycosis).

The most widely discussed infection is reactivation of latent TB. One study from the AERS (FDA Adverse Event Reporting System)[76] examined all reports of TB worldwide in patients on infliximab. Of the approx 147,000 patients who had been on the drug to date, there were 70 reported cases. Countries of high incidence were not over-represented. Interestingly, there was an unusually high likelihood of the extra-pulmonary manifestations of TB among infliximab-treated patients. Otherwise, most infections attributed to infliximab are common bacterial infections. There have also been notable increases in the incidence of listeriosis[77] and hepatitis B.[78]

In September 2008 the FDA released a statement to notify healthcare professionals regarding an increased risk in the development of invasive fungal infections such as histoplasmosis, coccidiomycosis, and blastomycosis.[79] In ACT 1 and ACT 2,[54] the incidence of infections was similar among all groups (ranging 2% to 4.5%), and included one patient who developed tuberculosis (on infliximab 10 mg/kg) and another who developed histoplasma pneumonia (5 mg/kg infliximab).

Malignancy

The first concerns of malignancy driven by anti-TNF were discussed in a case series published in 2002[80] of 26 cases of lymphoproliferative disorders following treatment with etanercept or infliximab. Bongartz et al[75] published a large meta-analysis of trials involving infliximab and adalimumab in RA and noted a pooled OR for malignancy of 3.3 (95% CI 1.2 to 9.1). With this in mind, other studies have failed to prove a direct relationship between anti-TNF and malignancy. One such study in patients with RA[81] found an equally increased risk of malignancy among RA patients taking and not taking anti-TNF therapies, suggesting rather that the underlying disorder or concomitant therapies may be driving malignant transformation.

Siegel et al[82] published data on a meta-analysis comparing Crohn's patients on anti-TNF to population (SEER) data

and Crohn's patients on thiopurine immunosuppressants (6-MP, azathioprine), looking specifically at the incidence of non-Hodgkin's lymphoma (NHL). They found an overall NHL incidence of 6.1 per 10,000 patient-years in patients on anti-TNF, which compares to an incidence in the normal population of 1.9 per 10,000 patient-years. This significant increase in NHL risk becomes less apparent when we compare data by Kandiel et al[83] which showed the observed rate of NHL in Crohn's patients on immunomodulators alone of 3.6 per 100,000 patient-years. Overall, this suggests a modest increase in lymphoma risk in patients on anti-TNF therapy. More specific concerns arise about hepato-splenic T-cell lymphoma (HSTCL) in young patients on infliximab; 8 cases have been reported over an 8-year period (1998 to 2006) to the FDA,[84] all of which were fatal. A further 8 IBD cases (and 1 RA patient) have since been reported to the FDA AER scheme, including 3 cases involving adalimumab.[85] Of note, all 16 cases were being concomitantly treated with immunosuppressants, either 6-MP or azathioprine.

A recent alert from the FDA (Aug 4 2009)[86] reported an increased risk of leukemia in patients treated with anti-TNF therapies, reflecting 147 postmarketing reports of leukemia in all patients, including adults, using anti-TNF therapy. Again, the same article notes that 61% of cases of malignancy reported occurred in patients that were concomitantly on azathioprine/6-MP or methotrexate.

Anti-TNF therapies have also been implemented in skin cancers- one study[87] reported an odds ratio of 1.5 (95% CI 1.2 to 1.8) for nonmelanoma skin cancers. Various malignancies were reported in the follow-up period of ACT 1 and ACT 2,[54] including prostate adenocarcinoma (1 patient), basal cell carcinoma (2 patients), colonic dysplasia (1 patient), and rectal adenocarcinoma (1 patient). Though some of these may be incidental findings, long term follow-up studies will determine if the association with infliximab is confirmed.

Antibody formation

A concern arises about the formation of antibodies to infliximab; described as human anti-chimeric antibodies, or ATIs. This has not been studied extensively in UC, though studies in Crohn's disease are helpful; Baert et al[88] evaluated antibody formation in 125 patients with Crohn's disease on episodic infliximab therapy and assessed patients for side effects and loss of effect. Sixty-one percent (76 patients) were shown to have detectable antibodies during the study period, though notably incidence did not increase with repeated infusions. Patients on concomitant immunosuppressive therapy (eg, azathioprine) had a lower incidence of antibody formation (43%) compared to those not on immunosuppressants (75%). The cumulative incidence of infusion reactions was 27%, and the occurrence of such a reaction strongly correlated with the concentration of antibodies against infliximab. Notably, there was also a clear negative relationship between the concentration of antibodies against infliximab and the duration of response to infliximab. The median duration of response among patients with low (<8 μg/mL) antibody concentrations was 71 days (95% CI 57 to 88) compared to those who had a high antibody concentration (>8 μg/mL) who had a median duration of response of 35 days (95% CI 28 to 42) ($P < 0.001$).

However, more recently, Maser et al[89] took the focus away from antibody formation and placed more emphasis on infliximab trough levels; Maser evaluated antibody formation and trough serum infliximab levels in 105 patients with Crohn's disease who were starting infliximab therapy. 82/105 (78%) of these were scheduled every 6 to 8 weeks as maintenance, whereas 23/105 (22%) were episodic. After a median of 14 infusions, 21% of patients had detectable antibodies (a further 54% were antibody "inconclusive"). Antibody formation was higher among patients undergoing episodic therapy (39%) than those undergoing maintenance therapy (16%) ($P = 0.036$) and was associated with a higher rate of infusion reactions (50% vs 21%; $P = 0.018$). However, the median durations of interval clinical remission between infusions were not different between antibody positive patients and antibody-negative patients who had an undetectable serum infliximab concentration (66% vs 67%). In contrast, a positive relationship was found between the serum concentration of infliximab and both the interval clinical remission ($R2 = 0.61$; $P < 0.001$), and the change in endoscopic score from baseline ($R2 = 0.46$; $P < 0.001$). Overall, the rate of clinical remission was higher in patients with a detectable infliximab trough level regardless of the presence of antibodies to infliximab.

Impact of infliximab on postcolectomy complications

Another important issue is whether patients who undergo colectomy on infliximab suffer from more postoperative complications. This question was addressed in two studies. Mor et al[90] performed a case-matched retrospective study of postoperative complications after restorative proctocolectomy (RP) between 2000 and 2006 in UC patients who were and were not treated with infliximab. In this time period, 46 cases were patients on infliximab who underwent a two-stage RP, who were then compared to infliximab-naive UC

controls who also underwent two-stage RP. Extent of UC and inflammatory markers were similar in these groups. Overall prevalence of early postoperative complications (eg, sepsis, leak, postoperative hemorrhage, ileus, thrombosis) was 16/46 (35%) in the infliximab group compared to 7/46 (15%) in the infliximab-naïve group ($P = 0.027$). Late postoperative complications (eg, pouchitis, stricture, small bowel obstruction) occurred in 24/46 (52%) of the infliximab group compared to 17/46 (37%) in the infliximab-naïve group ($P = 0.23$).

A similar study[91] involving the records of 47 UC patients who had received infliximab prior to RP compared to 254 UC patients who were infliximab-naïve. Surgical morbidity was similar between the groups (62% for infliximab-treated vs 49% for infliximab-naïve patients, $P = 0.1$), though anastomotic leaks ($P = 0.02$), pouch-specific disease ($P = 0.01$) and infectious complications ($P < 0.01$) were more common in the infliximab group.

These studies raise concerns that giving infliximab may increase the risk of post-operative complications. Unfortunately, the retrospective nature of these studies raises concerns about selection bias; the infliximab cohort may be an inherently sicker group and may have been immunosuppressed by concurrent immunosuppressive drugs for a longer period of time than the control populations selected.

Other adverse events

Infliximab has been associated with the development or worsening of demyelination in some studies. One study examining the occurrence of demyelination in patients on anti-TNF therapies as reported to the FDA AERS[92] identified 19 cases of demyelination in the arthritides (17 with etanercept, 2 with infliximab) – the paper noted that to date (2001), 77,152 patients were receiving etanercept, implying an incidence of demyelination of 31 per 100,000 patient years in etanercept-treated patients, compared to 4 to 6 per 100,000 per year in the general public. Of note, in follow-up data from ACT 1 and ACT 2,[54] 3 neurological events occurred, all in infliximab-treated patients; 2 patients developed optic neuritis, and 1 patient developed a multifocal motor neuropathy.

Finally, a randomized, double blind, placebo-controlled trial of infliximab in patients with moderate to severe heart failure (the ATTACH trial)[93] to assess its efficacy in treating heart failure actually found it to worsen the clinical condition in patients with severe heart failure. Thus, in patients with NYHA class III–IV heart failure, infliximab is considered relatively contraindicated.

Steps to reduce the risk of adverse events

Infusion reactions are relatively uncommon, and infliximab infusions are generally well tolerated. If a mild reaction occurs, future infusions can be pre-medicated with diphenhydramine and acetaminophen or a non-sedating antihistamine.[71] In order to reduce the risk of morbidity from tuberculosis, patients should be tested for latent TB with an intradermal PPD (tuberculin antigen) test.[94] Most physicians also perform a chest X-ray prior to initiating therapy. Also, we test at-risk groups for chronic hepatitis B. In addition, all patients should have regular follow-up by their gastroenterologist, and receive appropriate vaccinations against viral and bacterial infections; the Centers for Disease Control recommends an influenza, H1N1, pneumococcus, and hepatitis B vaccination in at-risk individuals receiving immunosuppression.[95,96]

Patient-focused perspectives

Adherence

Our understanding of medication adherence in patients with UC is mostly based on the use of mesalamine. Kane et al[97,98] have documented adherence rates in patients with UC, and reported that only 40% of patients were found to be adherent with mesalamine, and the median amount of medication consumed was 71% of the prescribed amount. This was primarily attributed to the pill burden of mesalamine compounds. Medication non-adherence in UC was shown to have a detrimental effect on patient wellbeing, with a 5-fold increased risk (61%) of disease relapse compared to those who were adherent (11%; $P = 0.001$).

In contrast, infliximab non-adherence in patients with Crohn's disease has been reported to be as low as 4%, and was associated with time since initial infusion and female gender in a multi-variate analysis.[99] Patient out-of-pocket costs may also influence adherence to anti-TNF agents such as infliximab.[100] In patients with RA, infliximab adherence is superior to that of methotrexate and sulfasalazine, and similar to that of adalimumab.[101] Overall, it appears that non-adherence with infliximab is not a major issue for patient treatment.

Quality-of-life

Quality of life (QoL) is an important endpoint that mirrors a patient's response to a drug, encompassing both the therapeutic effects of the drug, and the side effects created by the drug. The QoL model in UC focuses on 3 areas, namely physical function (loose stools, rectal bleeding, abdominal pain),

emotional function (anger, embarrassment), and social function (absenteeism, effects on social gatherings).[102]

The impact of UC on patients' QoL has recently been assessed from data derived from the PODIUM study (Pentasa Once Daily In UC for Maintenance of Remission)[103] using the UC-DAI (Ulcerative Colitis Disease Activity Index) as a standardized marker. Patients with mild/moderate UC had a health-related utility comparable to those with cardiac dysrhythmia or gout (mean utility of 0.775 vs 0.774 or 0.771 respectively). Furthermore, patients with severe relapsing UC had a similar utility to those with emphysema or renal failure (mean utility of 0.660 vs 0.663 or 0.651 respectively).

QoL related to anti-TNF use in UC patients has been addressed in only a small number of the studies discussed above. And considering it is a relatively novel therapy in this disease, long-term data are limited. To a certain extent, for now one must extrapolate from short-term data while indeed being mindful of the fact that the very patients in a UC cohort that receive infliximab are a sicker cohort of patients. For example, the Norwegian IBD cohort study that examined immunosuppressive use in UC identified a deterioration in QoL,[104] though again this may have reflected a selection bias, ie, a selection of inherently sicker UC patients.

In the ACT 1 and ACT 2 trials above,[54,105] a total of 728 patients randomized to either infliximab or placebo also provided data to assess QoL by way of the Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) and Medical Outcomes Study 36-Item Short Form Health Survey Physical and Mental Component Summary (PCS, MCS). At 8 weeks the IBDQ score was significantly higher (better) in both infliximab groups (5 mg/kg, 10 mg/kg) than placebo (40 and 36, respectively, compared to 28, $P < 0.001$). This was mirrored by equally positive results using the PCS and MCS scores. This benefit was sustained throughout the follow-up period of 1 year. Notably, patients who achieved remission had QoL scores close to population norms. Furthermore, mucosal healing inferred a greater QoL benefit than in patients who did not demonstrate mucosal healing.

Alternatives to infliximab

In patients with moderate to severe UC, a number of existing and novel therapeutic options exist. Azathioprine/6-MP and methotrexate are all efficacious in this patient population, although robust RCT evidence to support their use is lacking.

Azathioprine, 6-MP, methotrexate

Patients with moderate-severe UC requiring oral steroids, or who have failed 5-ASAs, have traditionally been treated with azathioprine/6-MP to maintain remission. The data to support this strategy is weak, as results from controlled trials have reported conflicting results, and only enrolled patients with severe or steroid-dependent disease.[106] A meta-analysis of 6 of these studies concluded that azathioprine was superior to placebo for maintenance of remission in UC.[107] Similarly, the only RCT to examine methotrexate in this setting showed no benefits, despite efficacy in open-label studies.[108,109]

Cyclosporine

Cyclosporine, on the other hand, has clear short-term efficacy in patients with severe or steroid-refractory UC. Lichtiger et al[110] conducted a small placebo-controlled trial that provided evidence in support of cyclosporine use in acute severe UC; 9 of 11(82%) patients with severe steroid-refractory UC randomized to iv cyclosporine responded, whereas none of the placebo group improved. Other studies have also reported short term response rates of 85% and 86% in steroid-refractory patients with UC.[111,112] Despite these high initial response rates, one of the limitations in cyclosporine's use has been the variable long-term colectomy rates. In Cohen et al's[112] study of steroid-refractory UC, 72% of cyclosporine-responders avoided colectomy after a median 5.5 years follow-up, particularly if they transitioned to azathioprine/6-MP (80% colectomy-free). In contrast, other studies have reported that up to 88% of patients required colectomy within 7 years of being treated with cyclosporine.[113] The cumulative data suggest that cyclosporine is an effective option in patients with steroid-refractory UC who are naïve to azathioprine/6-MP and can thus transition to these agents to enhance its long-term colectomy-sparing effects.

The other disadvantage of using cyclosporine is its side-effects, which limit long-term use. These include renal impairment, hypertension, tremor, seizures and infections. Sternthal et al[114] reviewed the records of 111 patients treated with cyclosporine for IBD over a mean treatment duration of 9 months; nephrotoxicitiy occurred in 5% and serious infections in 6%. Seizures, anaphylaxis and 2 deaths were also reported. Minor events included paresthesias in 51%, hypomagnesemia in 42%, hypertension in 39%, hypertrichosis in 27% and abnormal liver tests in 19%.

Other agents

Other anti-TNF agents under investigation for moderate to severe UC include adalimumab, certolizumab and golimumab. In patients with steroid-refractory disease, the efficacy of both basiliximab and visilizumab were disappointing in initial trials, and other agents have been examined only anecdotally.[115]

Finally, colectomy and end-ileostomy, or ileal pouch anal anastomosis (IPAA) always remain an option for patients with severe disease who have failed conventional therapies. A colectomy removes the risk of colon cancer, and the need for maintenance medications. Most patients can expect 6 to 8 stools per day with a successful IPAA. Pouchitis is the most commonly occurring long-term complication of IPAA, and occurs in 20% to 50% of patients over the life of the pouch.[116–119]

Conclusions

In patients with moderate to severe UC, infliximab is an effective therapy which provides an additional therapeutic option for these patients. Those patients with *moderate* disease who do not require hospitalization or iv steroids now have the options of treatment with either infliximab, or oral steroids as a bridge to azathioprine/6-MP. There appears to be a modest reduction in the risk of colectomy from infliximab over 1 year in patients with moderate to severe disease, but the overall colectomy rate is low (10% to 17%). Whether concomitant azathioprine/6-MP improves long-term outcomes with infliximab in UC is unknown; the colectomy rates in ACT 1 and ACT 2 were independent of azathioprine/6-MP use over 1 year. A UC equivalent of the SONIC trial would be required to address these questions.[120]

In patients with *severe*, or *steroid-refractory* UC, there are insufficient data to conclude whether iv infliximab or iv cyclosporine is the best approach. Cyclosporine is associated with higher initial response rates than infliximab, and at earlier time-points; 82% response within 7 days with cyclosporine, compared with 50% response at 2 weeks with infliximab.[48,110] The long-term colectomy-sparing rates with cyclosporine are often criticized, but if one looks at the sparse data in similar populations treated with infliximab, they are not that different. Within 2 years, 46% of patients treated with infliximab in the Jarnerot study had undergone a colectomy, compared with a 51% colectomy rate in Lichtiger's cohort treated with cyclosporine.[51,121] Only an ongoing direct comparison randomized controlled trial will answer this critical question. Our personal practice is to use cyclosporine in steroid-refractory patients with UC who are azathioprine/6-MP-naïve, and reserve infliximab for those who have already failed azathioprine/6-MP, or have contra-indications to cyclosporine. When steroid-refractory patients fail infliximab, we feel the small amount of data published to date suggest that the modest benefits gained by adding cyclosporine need to be considered in light of the higher initial risk of serious adverse events of "triple" immunosuppression.

It appears likely that expanded use of infliximab may lead to more patients with severe disease retaining their colon for longer periods of their lives. This advantage will require an increased vigilance for dysplasia and cancer development during follow-up.[122]

Disclosures

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