

The safety and efficacy of antitumour necrosis factor- α therapy for inflammatory bowel disease in patients post liver transplantation: a case series

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SUMMARY

Background

The role of antitumour necrosis factor- α (anti-TNF) therapy for inflammatory bowel disease (IBD) among liver transplant recipients is largely unknown given the rarity of this population and the paucity of literature on the subject.

Aim

To investigate the safety and efficacy of anti-TNF therapy for refractory IBD in the post liver transplant population.

Methods

The liver transplant database at London Health Sciences Centre was searched to identify adult patients with IBD treated with anti-TNF therapy post transplantation.

Results

Six patients (five men, one woman) were identified, aged 28–65. All patients had cadaveric orthotopic liver transplants. Four patients required transplantation due to primary sclerosing cholangitis, one due to autoimmune hepatitis, and one due to biliary atresia. Five patients suffered from Crohn's disease and the remaining patient from indeterminate colitis. All patients were treated with infliximab 5 mg/kg every 8 weeks after undergoing induction at weeks 0, 2 and 6, with the exception of one patient. The duration of infliximab therapy ranged from 8 weeks to 4 years. Four patients treated with infliximab experienced sustained improvement of their IBD symptoms post transplantation, as documented by Harvey–Bradshaw Index scores demonstrating clinical remission. Of the remaining two patients, neither had sustained improvement of their IBD with infliximab or subsequent adalimumab. One patient was diagnosed with systemic lupus erythematosus and another with colorectal adenocarcinoma following anti-TNF therapy. Otherwise, no side effects were attributed to anti-TNF therapy.

Conclusions

Based on this case series, anti-TNF therapy appears to be safe and effective for treating refractory IBD in patients post liver transplantation. These patients respond to anti-TNF therapy similar to those who have not been previously transplanted.

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INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory disorders of the gastrointestinal tract that includes both Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease is a segmental, transmural, granulomatous disease of unknown aetiology that often results in sinus tracts that breach the serosa and create microperforations, fistulae and abscesses. Ulcerative colitis, in contrast, is characterised by recurring episodes of inflammation limited to colonic mucosal layer that is usually continuous in nature and almost always originates in the rectum, and ascends proximally throughout the colon as the disease progresses.

Tumour necrosis factor- α (TNF) has a central role in the pathogenesis of the mucosal inflammation of both CD and UC. Anti-TNF therapy, including infliximab, adalimumab, and certolizumab, has been a key introduction to the treatment regimen of UC and CD refractory to more conventional therapies, such as aminosalicylates, corticosteroids and immunomodulators.¹

However, the role of anti-TNF agents in controlling IBD in liver transplant recipients is much less clear given the rarity of this population and the paucity of literature on the subject. This case series investigates the safety and efficacy of anti-TNF therapy for refractory IBD among liver transplant recipients. One isolated case report exists, which documents the safe and efficacious use of infliximab in controlling symptoms of UC post-orthotopic liver transplantation (OLT).²

METHODS

We performed a retrospective search of the liver transplant database at London Health Sciences Centre to identify adult patients who underwent orthotopic liver transplantation between January 1990 and September 2011. Retrospective chart analysis was approved by the Western University Research Ethics Board. Liver transplant recipients from our centre were subsequently reviewed to identify those who received anti-TNF therapy for IBD at any time after transplantation. Patients who received anti-TNF therapy prior to transplantation and continued or restarted this treatment following transplantation were also included in the study.

These patients were reviewed to identify the indication for liver transplantation and their associated immunosuppressive regimen following surgery, the type of IBD they suffered from, the natural history of the disease following transplantation, the dosing and duration of anti-TNF therapy used and finally the clinical response and adverse reactions to this therapy. Clinical response was

assessed using the Harvey–Bradshaw Index (HBI),³ where clinical remission was defined as a score of <5 . Clinic and hospital notes were used to determine IBD symptoms prior to and after anti-TNF therapy to retrospectively calculate the HBI scores.

RESULTS

Six patients (five men, one woman; age range of 28–65 years) were identified (Table 1). The mean age at the time of data collection was 49.0 years and the mean age at time of transplantation was 41.3 years. All patients had cadaveric OLT. Four patients required transplantation due to primary sclerosing cholangitis (PSC), one due to autoimmune hepatitis (AIH), and one due to biliary atresia. With respect to their IBD, five patients had confirmed diagnosis of CD. Of these, three were initially suspected to have UC, however, following OLT, all three patients developed active ileitis and were diagnosed with CD based on ileocolonoscopy and biopsies. The remaining sixth patient had pancolitis on colonoscopy but with granulomas on biopsies and was deemed to have indeterminate colitis. Three patients were diagnosed with IBD prior to transplantation and three after transplantation.

Of the six patients, all were treated with infliximab 5 mg/kg every 8 weeks after undergoing induction at weeks 0, 2 and 6, with the exception of one patient who received her third dose at week 10 due to appointment cancellation. The duration of infliximab therapy ranged from 8 weeks to 4 years at the time of data collection. Four patients (67%) treated with infliximab experienced sustained improvement of their IBD symptoms post transplantation, with improved abdominal pain and decreased frequency and increased consistency of bowel movements. Of these four patients, HBI scores prior to anti-TNF therapy ranged from 10 to 13, and after anti-TNF therapy, three of the four had an HBI score of 0 and one had an HBI score of 1. This latter patient was given a score of 1 as he developed arthralgias after over 1 year of clinical remission with anti-TNF therapy. This was likely attributed to a new diagnosis of systemic lupus erythematosus (SLE) after 16 months of infliximab.

Of the remaining two patients, one lost response after 16 months of infliximab therapy (case 2) and ultimately required a colectomy and ileo-anal pouch procedure. He experienced continued symptoms 1 year post-operatively and active ileitis was discovered. He was then started on adalimumab due to these unremitting symptoms, but his condition failed to improve despite dose escalation from 40 mg every other week to 40 mg weekly. Accordingly,

Table 1 | Case series of patients treated with anti-TNF therapy for IBD post-orthotopic liver transplantation

Liver transplant history				IBD history								
Aetiology of hepatic pathology				Diagnosis of IBD pre- or post-OLT								
Case	Age	Gender	Antirejection treatment regimen	IBD type	Anti-TNF	Dosing and duration of anti-TNF treatment	Pre-anti-TNF HBI	Post-anti-TNF HBI	Adverse events related to anti-TNF therapy			
1	65	Male	AIH	55	Tacrolimus 1 mg in am & 0.5 mg in pm, MMF 1 g BID, Prednisone 5 mg daily	Indeterminate colitis: Pancolitis with rectosigmoid sparing but granulomas on biopsy.	Post	Infliximab	5 mg/kg; Induction at weeks 0, 2 and 6, then 5 mg/kg infusions every 8 weeks for 13 months, still on therapy.	10	0	None
2	38	Male	PSC	31	Tacrolimus 1 mg PO BID	Crohn's Disease: Originally diagnosed as UC; following colectomy, had recurrent pouchitis and ileitis, with biopsies confirming CD.	Post	Infliximab then adalimumab	Infliximab: 5 mg/kg; Induction at weeks 0, 2 and 6, then 5 mg/kg infusions every 8 weeks for 16 months, then lost response. Adalimumab: 40 mg SC every other week for 6 weeks then weekly for 2 months, still on therapy.	17	Post infliximab: 12 Post adalimumab: 13	None
3	46	Male	PSC	37	Tacrolimus 4 mg BID, MMF 500 mg BID, Prednisone 50 mg daily (tapering)	Crohn's Disease	Pre	Infliximab	5 mg/kg; induction at weeks 0, 2 and 6, then 5 mg/kg infusions every 8 weeks for 5 months, still on therapy.	11	0	None
4	60	Male	PSC	53	Tacrolimus 0.5 mg BID, MMF 500 mg BID	Crohn's Disease: Originally diagnosed as UC; but after colectomy and ileo-anal pouch, developed peri-anal abscess, fistula-in-ano, and granulation tissue in terminal ileum.	Pre	Infliximab	5 mg/kg; Induction at weeks 0, 2 and 6, then 5 mg/kg infusions every 8 weeks for 16 months; therapy discontinued.	11	1	New diagnosis of systemic lupus erythematosus
5	28	Male	Biliary Atresia	21	Cyclosporine 100 mg BID, Azathioprine 200 mg daily	Crohn's Disease: complicated by fistulising disease.	Post	Infliximab	5 mg/kg; Induction at weeks 0, 2 and 6, then 5 mg/kg infusions every 8 weeks for 49 months, still on therapy.	13	0	None
6	57	Female	PSC	51	Tacrolimus 2 mg daily, MMF 250 mg BID, Prednisone 5 mg daily	Crohn's Disease: Initially diagnosed with UC, however subsequent colonoscopies revealed evidence of discrete ulcerations and terminal ileitis.	Pre	Infliximab then adalimumab	Infliximab: Induction at weeks 0, 2 and 10, then 5 mg/kg infusions every 8 weeks for 3 months then discontinued therapy. Adalimumab: 40 mg SC every other week for 3.5 months then discontinued therapy.	14	Post infliximab: 16 Post adalimumab: 14	New diagnosis of colorectal adenocarcinoma

his HBI scores improved only mildly following anti-TNF therapy. The other patient (case 6) had no clinical response following induction with infliximab nor after 3.5 months of adalimumab therapy. Her HBI scores did not show improvement following anti-TNF therapy.

Of the six patients, anti-TNF therapy was tolerated well. There were no reports of any acute side effects, including infections. Case 2 developed symmetrical inflammatory polyarthritis, Raynaud's syndrome and a pericardial effusion secondary to pericarditis in addition to strongly positive autoantibody titres, indicative of a new diagnosis of SLE. This was after nearly 16 months of successful infliximab therapy. However, the time course of events suggested that the polyarthritis likely predated infliximab use but a new diagnosis of primary SLE in a 60-year-old man was unusual and the infliximab was temporarily discontinued as a result. Case 6 was ultimately diagnosed with colonic adenocarcinoma following proctocolectomy for dysplasia found at colonoscopy after two short courses of both infliximab and adalimumab (Table 1).

With respect to the liver transplants, five of six patients had good outcomes with appropriate liver synthetic function and no evidence of rejection or recurrence of disease at the time of chart review. One patient, case 2, experienced recurrence of his PSC. He was also one of two patients in this study who lost response to anti-TNF therapy, as mentioned earlier.

DISCUSSION

This case series was designed to study the safety and efficacy of anti-TNF therapy for IBD in liver transplant recipients. In our study, 67% of patients experienced significant improvement of their symptoms following induction and maintenance with infliximab therapy. Patients experienced improved abdominal pain, reduced frequency of their bowel movements and of those containing blood and increased consistency of their bowel movements. Their HBI scores improved dramatically as they achieved clinical remission. The remaining 33% of patients did not have sustained response with infliximab or, subsequently, with adalimumab. These results are similar to what was found in subjects who have not previously undergone an orthotopic liver transplant.⁴⁻⁶ Case 1 was diagnosed with indeterminate colitis by his treating gastroenterologist as this patient had pancolitis with rectosigmoid sparing, but granulomas on biopsy. He was the only patient in this case series not definitively diagnosed with CD. However, the presence of granulomas and rectal sparing suggested a

diagnosis of CD, so he was included in our HBI calculations and had dramatically improved symptoms with anti-TNF therapy, irrespective of the scoring system utilised.

Given the rarity of this population, little evidence exists as to the optimal treatment strategy for IBD post transplantation. As part of their initial immunosuppressive regimen, corticosteroids are used for prevention of solid organ rejection. Corticosteroids are also effective for treating active IBD, but generally do not lead to mucosal healing or maintenance of remission.⁷ Calcineurin inhibitors, such as cyclosporin or tacrolimus, are used as long-term immunosuppressive therapy in solid organ transplantation but have conflicting evidence for treating IBD.⁸⁻¹³

Mycophenolate mofetil (MMF) is also used as long-term immunosuppressive therapy, but it is not clearly beneficial for treating IBD.¹⁴ Mycophenolate mofetil is often also associated with gastrointestinal side effects, such as diarrhoea, which may limit its utility in treating IBD among liver transplant recipients. In the past, 6-mercaptopurine and azathioprine (which are both effective in treating IBD) were among the first antirejection medications used in OLT patients. They are now less favoured due to the adverse effects of cytopenias and hepatotoxicity associated with the doses required to produce adequate antirejection therapy, in addition to the advent of other efficacious agents.^{15, 16} Other evidence suggests that the introduction of infliximab therapy, when cyclosporin has failed to induce or maintain remission, may be beneficial in those with severe corticosteroid-refractory IBD.¹⁷ However, little literature exists on controlling IBD in the post transplant population.

Several potential adverse effects exist with anti-TNF therapy, many of which must be differentiated from not only the baseline risk in IBD patients, but also from the increased risk that may exist in the already immunosuppressed solid organ transplant population. These side effects include injection site or infusion reactions¹⁸ which have the risk of developing into severe systemic anaphylactic reactions,¹⁹ cytopenias including neutropenia,²⁰ infections^{21, 22} including reactivation of latent viruses,²³⁻²⁶ demyelinating diseases,²⁷⁻³⁰ heart failure,³¹ and granulomatous and interstitial pulmonary disease.³² Patients treated with anti-TNF therapy also have an increased incidence of forming autoantibodies, particularly antinuclear antibodies or antidouble stranded DNA antibodies,³³ in addition to development of autoimmune diseases such as vasculitides³⁴ and SLE.³⁵ It is unclear

whether immunosuppression, like anti-TNF therapy, creates a new risk of autoimmunity in this population or accelerates a predisposed risk. One patient in this case series developed symptoms suggestive of SLE after nearly 1 year of infliximab therapy. No patient in our case series experienced any other of the aforementioned adverse effects secondary to anti-TNF therapy.

Another concerning risk is that of malignancy, which remains controversial given the difficulty of establishing causality, although in some cases a clear risk has been established.³⁶ Numerous observational and retrospective studies, meta-analyses and systematic reviews have examined the risk of lymphoma,^{37–39} solid organ malignancies^{40, 41} and skin cancers^{42, 43} secondary to anti-TNF therapy but with no clear association. This must be differentiated from the risk of malignancy that inherently exists in the solid organ transplant population, the most common of which include skin cancers (usually squamous cell carcinomas), anogenital cancers, renal cell carcinoma, hepatocellular carcinoma (which could be related to chronic liver disease), cancers of the upper respiratory tract and the oral pharynx, sarcomas and other solid organ tumours. Risks can vary depending on the specific immunosuppressive regimen used, in addition to other independent risk factors, such as the coexistence of other viral infections, patient history of other malignancies, and sun exposure.⁶

The coexistence of refractory IBD in an already immunosuppressed transplant population thus creates a therapeutic dilemma as to whether an additional immunosuppressant, such as an anti-TNF agent, should be added to the patient's treatment regimen. Such an addition could theoretically potentiate the adverse effects of long-term immunosuppression, including that of malignancy, but there is a paucity of evidence to support this. In our case series, case six ultimately developed stage IIIB multifocal adenocarcinoma of the colon which was found in the colectomy specimen following surgery for known dysplasia. This was after failed induction of infliximab and over 3 months of ada-

limumab therapy. However, her adenocarcinoma was also in the setting of a 15-year history of Crohn's colitis and over 7 years of immunosuppression following liver transplantation, both of which increase the risk of malignancy. Otherwise, in our case series, there were no reports of malignancy developing after OLT and after anti-TNF therapy.

The natural history of IBD post-OLT is not well understood. Some studies have suggested that the course of IBD can be aggressive despite immunosuppression^{44–48} while other studies suggest an unchanged or improved natural history,^{49, 50} although much of the literature focuses on UC. In this case series, three patients were also diagnosed with IBD de novo, post-OLT. Numerous case reports have shown a particular predilection for IBD to occur de novo post-OLT as opposed to transplantation of other organs, but the pathogenesis of this remains unclear, with one study documenting the success of oral budesonide in the treatment of de novo IBD.^{51, 52} Inflammatory bowel disease is also associated with both PSC and AIH, both of which are very common indications for transplantation and comprised the aetiologies of liver disease for all but one patient in this case series. Treatment of IBD post-OLT has not been described in any prospective studies, but many of the above studies documenting the natural history of the disease describe its management using traditional therapeutics, such as salicylates, with variable success.

To our knowledge, the use of anti-TNF therapy in refractory IBD among liver transplant recipients has been reported only rarely. In our case series, we found that patients generally responded favourably to anti-TNF therapy and similarly to those who have not previously been transplanted. Although there still is some potential for significant adverse events, in post-OLT patients with severe IBD, anti-TNF therapy can be used safely and effectively in the majority of cases.

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