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Anti-tumour necrosis factor treatment of inflammatory bowel disease in liver transplant recipients

A. B. Mohabbat*, W. J. Sandborn†, E. V. Loftus Jr‡, R. H. Wiesner‡ & D. H. Bruining‡

*Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA.
†Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA.
‡Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Correspondence to:
Dr D. H. Bruining, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First Street, SW, Rochester, MN 55905, USA.
E-mail: bruining.david@mayo.edu

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SUMMARY

Background
Ulcerative colitis (UC) and Crohn's disease can sometimes relapse and be refractory to standard treatment following orthotopic liver transplantation (OLT) despite post-transplantation immunosuppressive therapy.

Aim
To evaluate the efficacy and safety of anti-tumour necrosis factor (anti-TNF) agents for the management of IBD following OLT.

Methods
We reviewed the records of patients with a diagnosis of IBD who underwent OLT at Mayo Clinic Rochester between 1985 and 2009. Patients were included if they had received anti-TNF therapy post-OLT. Clinical response was defined as a physician's assessment of improvement after 12 weeks of anti-TNF usage, and mucosal healing was defined as the absence of ulcerations on follow-up endoscopy.

Results
The median age of the eight study patients was 42.0 years and 37.5% were female patients. All had been diagnosed with IBD prior to OLT (UC in three and Crohn's disease in five). Indication for OLT was cirrhotic stage primary sclerosing cholangitis (PSC), and three concomitantly had cholangiocarcinoma. Clinical response was demonstrated in seven of eight patients (87.5%) and mucosal healing was demonstrated in three of seven (42.9%). Four infections (oral candidiasis, *Clostridium difficile* colitis, bacterial pneumonia and cryptosporidiosis) in three patients were reported. One patient developed an Epstein–Barr virus-positive post-transplant lympho-proliferative disorder. One death occurred due to complications from recurrent PSC.

Conclusions
Starting Anti-TNF therapy following orthotopic liver transplantation appears to be a potential option for inflammatory bowel disease management. Additional studies are needed, however, to confirm these findings and to further assess risks associated with this treatment strategy.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease are chronic idiopathic IBD that can be associated with extraintestinal immune-mediated manifestations. It is estimated that 5% of IBD patients will develop primary sclerosing cholangitis (PSC).[1] This fibroinflammatory hepatobiliary disease frequently progresses to advanced liver disease requiring liver transplantation. There is a paucity of data regarding the medical management of IBD in patients who are status post orthotopic liver transplantation (OLT) when they require medical therapy in addition to their post-transplant immunosuppressive regimen. Some of these patients will experience a severe relapse of their IBD following OLT.[2–5]

Anti-tumour necrosis factor-alpha (anti-TNF) agents (infliximab, adalimumab and certolizumab pegol) have emerged as useful therapies for the medical treatment of moderate-to-severe IBD that is refractory to conventional therapy. In Crohn's disease, these drugs have been shown to be efficacious for both the induction and maintenance of remission, as well as for the treatment of perianal fistulas (infliximab) and ankylosing spondylitis (infliximab and adalimumab).[6–8] In UC, infliximab and adalimumab are effective for both induction and maintenance of remission.[9] Anti-TNF based regimes are now part of standard IBD management algorithms.[10, 11]

Despite the widespread use of anti-TNF agents, little is known about their efficacy or safety in patients with IBD following OLT.[12, 13] This can be an extremely challenging subset of patients to manage, given their medical complexity and immunocompromised status. We sought to further explore this issue, hypothesising that anti-TNF may be beneficial for IBD following OLT.

METHODS

A medical record search was performed to identify all patients with an established diagnosis of UC or Crohn's disease who underwent OLT at Mayo Clinic Rochester between 1 January 1985 and 31 December 2009 and who had received anti-TNF therapy following liver transplantation. Medical records were reviewed to obtain demographics and clinical information. The abstracted data included IBD subtype (UC, Crohn's disease, or indeterminate colitis), duration of IBD, past and current IBD therapies, presence of PSC and/or cholangiocarcinoma, indication for OLT and post-transplantation immunosuppressive regimen.

In-patient and out-patient medical records and endoscopy reports were also reviewed to determine clinical outcomes. Clinical response was defined as a physician's assessment of improvement after 12 weeks of anti-TNF administration, and mucosal healing was defined as the absence of ulcerations on follow-up endoscopy. Furthermore, the medical records were reviewed for any adverse events defined as opportunistic infections, graft dysfunction, infusion/injection reactions, or malignancy.

Descriptive statistics were reported as numbers (percent), ranges and medians as appropriate.

RESULTS

We identified eight patients with a diagnosis of IBD who underwent OLT with subsequent anti-TNF drug administration (Table 1). The median age was 42.0 years (range, 22.0–69.0 years). Men comprised 62.5% of the cohort. All eight patients had a diagnosis of IBD prior to OLT; three patients were diagnosed with UC, while five individuals were diagnosed with Crohn's disease. The median IBD disease duration was 17.0 years (range, 5.0–48.0 years). Six previous IBD-related surgical interventions had occurred in five patients, including subtotal colectomy with ileosigmoidostomy (n = 2), total proctocolectomy with ileostomy (n = 1) and total proctocolectomy with

Table 1 | Patient demographics and medical history

Subjects	N = 8
Median age (years)	42.0 (range 22.0–69.0)
Gender	62.5% men
IBD diagnosis prior to OLT	
Ulcerative colitis	3 (37.5%)
Crohn's disease	5 (62.5%)
Median IBD duration (years)	17.0 (range 5.0–48.0)
Indications for OLT	
PSC	8 (100.0%)
Cholangiocarcinoma	3 (37.5%)
Median duration PSC diagnosis to OLT (years)	7.0 (range 0.6–19.0)
Liver Donor Information	
Living donor	3 (37.5%)
Deceased donor	5 (62.5%)
Anti-TNF therapy prior to OLT*	3 (37.5%)
Median time to Anti-TNF usage after OLT (years)	3.5 (range 1.0–14.0)
Post-OLT Anti-TNF indication	
Diarrhoea	7 (87.5%)
Penetrating perianal disease	1 (12.5%)
Anti-TNF therapy post-OLT	
Infliximab	4 (50.0%)
Adalimumab	2 (25.0%)
Infliximab followed by Adalimumab	2 (25.0%)

* Two patients received infliximab and one received infliximab followed by adalimumab prior to OLT.

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ileal pouch-anal anastomosis (IPAA) (n = 3). Pre-transplant IBD therapies consisted of 5-aminosalicylate agents (n = 5), immunomodulators (n = 4) (azathioprine, mercaptopurine and/or methotrexate), corticosteroids (n = 6) and anti-TNF agents (n = 3). None of the patients had immunomodulators or anti-TNF therapy continued at the time of liver transplantation.

All eight patients underwent OLT due to advanced liver disease related to PSC, while three had a concomitant cholangiocarcinoma. Five of the liver transplant donors were deceased, while three were from living donors (donated to patients with cholangiocarcinomas). The median duration from diagnosis of PSC to liver transplantation was 7.0 years (range, 0.6–19.0 years). The protocol post-transplantation immunosuppressive regimen consisted of tacrolimus or cyclosporine, mycophenolate mofetil and prednisone (Table 2).

The median duration from OLT to anti-TNF alpha usage was 3.5 years (range, 1.0–14.0 years). Although three patients had previously received anti-TNF therapy prior to liver transplantation, no anti-TNF agents were continued at the time of transplantation. The indications for anti-TNF agents were diarrhoea/increased frequency of bowel movements (n = 7) and penetrating perianal disease (n = 1). Three patients with IPAAs received anti-TNF therapy. Indications were Crohn's disease of the pouch (n = 1, change in diagnosis from ulcerative colitis to Crohn's disease), and refractory pouchitis (n = 2). Anti-TNF agents administered post-OLT included infliximab (n = 4), infliximab followed by adalimumab (n = 2) and adalimumab (n = 2). The rationale for changing from infliximab to adalimumab included a severe infusion reaction and a case of secondary loss of response.

The mean duration of post-OLT follow-up was 6.4 years. Clinical response was demonstrated in seven of eight patients (87.5%) after initiation of anti-TNF therapy. Mucosal healing was demonstrated in three of seven patients (42.9%); at the time of our review, one patient had not completed a follow-up endoscopy. Of the six patients on corticosteroids at the time of anti-TNF initiation, five (83.3%) were able to taper off corticosteroids successfully. Of the two patients changed from infliximab to adalimumab, only one patient demonstrated clinical improvement. In those individuals treated with anti-TNF therapy pre-OLT (n = 3), two demonstrated clinical response and one had documented mucosal healing.

Adverse events included four infections in three patients while on anti-TNF therapy, including oral candidiasis, *Clostridium difficile* colitis, bacterial pneumonia and cryptosporidiosis. One individual developed an Epstein–Barr virus-positive polymorphic post-transplant lympho-proliferative disorder (PTLD) in the absence of depleting anti-lymphocyte therapy. This occurred 4 months after starting anti-TNF therapy and 4 years after OLT. This patient had been on anti-TNF therapy and 6-mercaptopurine in the pre-OLT period. The PTLD was successfully treated with rituximab. One individual developed an infusion reaction with infliximab. No organ rejection was documented while on anti-TNF therapy. One patient experienced a significant rise in hepatic biochemistries (tripling of serum alkaline phosphatase level) while on infliximab, and it was discontinued after four doses. This patient was later diagnosed with recurrent PSC. Recurrence of PSC was noted in a total of three patients, with no recurrence of cholangiocarcinoma at the time of last follow-up. One death occurred due to complications from recurrent PSC and biliary sepsis, approximately 2.4 years after the last dose of infliximab.

DISCUSSION

This study demonstrates that anti-TNF therapy for IBD following OLT appears to be of clinical benefit. These results corroborate the findings of previous small case reports in the literature.[12–14] Our study revealed a clinical response in 87.5% and mucosal healing in 42.9% of the cohort. Furthermore, 83.3% were tapered off corticosteroids successfully after starting anti-TNF therapy. No subsequent IBD-related surgical interventions were documented following initiation of anti-TNF therapy postliver transplantation.

We believe our manuscript nearly doubles the total reported cases of anti-TNF therapy use in OLT patients (Table 3). The previous largest case series (n = 6) was recently published by Sandhu and colleagues.[14] This study included six patients, five with Crohn's disease and one individual with indeterminate colitis. Only three individuals were diagnosed with IBD prior to liver transplantation. Response, as assessed using the Harvey-Bradshaw Index (HBI), was noted in 67% (n = 4). Our study, larger in size (n = 8) and with a more diverse population (three patients with ulcerative colitis, five patients with Crohn's disease and three patients with an IPAA), demonstrated a similar trend in terms of efficacy. We noted a clinical response in 87.5% (based on global physician clinical assessment) and mucosal healing in 42.9%. Unlike the study by Sandhu *et al.*, we did observe four infections and one lympho-proliferation disorder.

Table 2 | Medications at the time of post-OLT anti-TNF therapy

Patient	Anti-TNF agent	Calcineurin inhibitor	Corticosteroids	Immunomodulators	Others
1	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8 weeks	Tacrolimus 4 mg PO BID	Prednisone 20 mg PO qd	Azathioprine 50 mg PO daily	None
2	Adalimumab Induction: 160 mg SC week 0, 80 mg SC week 2 Maintenance: 40 mg SC every 2 weeks	Tacrolimus 3.5 mg PO BID	Prednisone 2.5 mg PO qd	None	5 ASA PO
3	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8	Tacrolimus 2 mg PO BID	None	None	None
4	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8	Tacrolimus 2 mg PO BID	Budesonide 9 mg PO qd	None	Mycophenolate mofetil 1000 mg PO BID
5	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8	Cyclosporine 150 mg PO qam 125 mg PO qpm	Prednisone 5 mg PO qd	None	5 ASA PO
6	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8; escalated to every 6 weeks before change to adalimumab	Tacrolimus 3 mg PO qam 2 mg PO qpm	None	Azathioprine 100 mg PO daily	None
	Adalimumab Induction: 160 mg SC week 0, 80 mg SC week 2 Maintenance: 40 mg SC every 2 weeks	Tacrolimus 2 mg PO BID	Prednisone 10 mg PO BID	Azathioprine 100 mg PO BID	None
7	Adalimumab Induction: 160 mg SC week 0, 80 mg SC week 2 Maintenance: 40 mg SC every 2 weeks	Tacrolimus 2 mg PO BID	Prednisone 5 mg PO qd	None	None
8	Infliximab Induction: 5 mg/kg weeks 0, 2, 6 Maintenance: 5 mg/kg every 8; dose escalation to 10 mg/kg before change to adalimumab	Cyclosporine 100 mg PO BID	None	Azathioprine 50 mg PO BID	None
	Adalimumab Induction: 160 mg SC week 0, 80 mg SC week 2 Maintenance: 40 mg SC every 2 weeks	Cyclosporine 100 mg PO BID	None	Azathioprine 50 mg PO BID	None

BID, twice a day; PO, oral; qd, daily; SC, subcutaneous.

Four patients developed infections post-OLT while on anti-TNF therapy, including oesophageal candidiasis, *Clostridium difficile* colitis, community-acquired bacterial pneumonia and cryptosporidiosis. All infections responded to antimicrobial therapy. These findings highlight the need for close monitoring and risk discussions with patients placed on anti-TNF therapy in this setting.

One patient developed an Epstein–Barr virus-positive polymorphic PTLD. The overall incidence of PTLD has been reported as 2%, with 67% developing PTLD within 1 year of transplantation (mean interval of 27 months).[15] It has also been noted from the RATIO (Research Axed on Tolerance of bIOtherapies) registry that there may be two to threefold increased risk of lymphoma in patients

Table 3 | Publications on anti-TNF therapy in OLT patients

First author	Journal & date	Number OLT subjects	Assessment scale	Outcome
A. Mohabbat	Aliment Pharmacol Ther	*N* = 8	Clinical Response & Mucosal Healing	Response: 87.5% Mucosal healing: 42.9%
A. Sandhu[14]	Aliment Pharmacol Ther 2012	*N* = 6	Harvey-Bradshaw Index (HBI)	Response: 66.7%
N. El-Nachef[13]	Am J Gastroenterology 2010	*N* = 3 (1 renal transplant)	Clinical Response	Response: 100%
S. Lal[12]	Eur J Gastroenterol Hepatol 2007	*N* = 1	Clinical Response & Endoscopic Improvement	Response: 100% Endoscopic Improvement: 100%

receiving anti-TNF therapy.[16] It is important to take these figures into account when considering the single case of PTLD in this study.

The recurrence of PSC was 37.5% in this group. While the presence of IBD is a risk factor for recurrent PSC, this is greater than the previously reported 20% rate of PSC recurrence after liver transplantation.[17, 18] We suspect this is related to the small number of patients in our analysis, but larger studies will be needed to further explore this finding.

The primary limitation of this study is its small size. Our search demonstrated only eight patients that met our inclusion criteria. Although this study is the largest to date, the results must be interpreted with caution given the small number of patients. It is impossible to fully define efficacy and risk with this sample size; however, the results provide useful information to physicians and patients, while also providing justification for further exploration and assessments. In addition, given the diverse nature of these patients (ulcerative colitis and Crohn's disease) and the various surgical procedures (three patients with IPAA), it is difficult to standardise the definition of response to anti-TNF therapy. We selected clinical response (global physician assessment) and mucosal healing (resolution of ulcerations). All patients who had an endoscopy prior to anti-TNF therapy had ulcerations. Mucosal healing was defined by the resolution of ulcerations, but we acknowledge that this definition may be less ideal in patients with ulcerative colitis and IPAAs.

In summary, our analysis suggests that anti-TNF therapy may be an effective option for IBD management following OLT. Potential risks include opportunistic infections and PTLD. Additional studies are needed to further evaluate the risks associated with this treatment strategy, and whether the risk of recurrent PSC is higher in patients receiving anti-TNF therapy in the post-OLT setting.

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