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Vedolizumab is Safe and Effective in Moderate to Severe Inflammatory Bowel Disease Following Liver Transplantation

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Keywords

Ulcerative colitis; biologic therapy; calcineurin inhibitor; Crohn's disease; opportunistic infection

To the Editor

The medical management of inflammatory bowel disease (IBD) in patients with advanced liver disease or after liver transplantation (LT) can be challenging due to the increased risk of bacterial and opportunistic infections. While anti-TNF agents are widely used in the treatment of moderate to severe IBD in the general population, they associated with an increased risk for systemic fungal infections, reactivation of hepatitis B and latent tuberculosis, and other opportunistic infections to which LT recipients are particularly susceptible [2]. LT recipients treated with anti-TNF agents have been reported to have several infections, post-transplant lymphoproliferative disorder, and drug-induced lupus [1].

Vedolizumab is an FDA approved humanized monoclonal antibody antagonist of the alpha$_4$-beta$_7$ integrin, used for the treatment of IBD. Alpha$_4$-beta$_7$ integrin blockade speficificalyl prevents leukocyte trafficking into gastrointestinal tissue. A very low (nearly nil) incidence of bacterial, mycobacterial, occult viral and other opportunistic infections as were reported in vedolizumab clinical trials and meta-analyses [3], [4]. Mounting safety evidence paired with a mechanism specifically targeting intestine suggests vedolizumab may offer an attractive option for moderate to severe IBD in solid organ transplant recipients. We report our institution's experience using vedolizumab in LT recipients with moderate to severe IBD.

Methods

Patients

A waiver of consent was provided by the local institutional review board to conduct a retrospective search of the electronic liver transplant database at the University of Michigan

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Conflict of Interest:

The authors have no potential conflicts of interest relevant to this manuscript to declare

Health System. Between January 2014 and March 2016 we identified adult LT recipients with a diagnosis of IBD and exposure to vedolizumab using an electronic medical record search tool (EMERSE) combined and manual chart review. The adult immunosuppressive regimen used in our center consists of tacrolimus, mycophenolate and tapering doses of corticosteroids. Selected individuals with renal insufficiency at the time of LT may receive basiliximab induction doses at days 1 and 4 with a delay in the initiation of tacrolimus to day 3 or 4. The target tacrolimus trough levels are 6 to 10 ng/ml through month 3 and 4 to 8 ng/ml thereafter. Corticosteroids are typically discontinued by month 3 in patients with viral hepatitis but maintained at 5 to 10 mg/day through year 1 in subjects with PSC and autoimmune liver disease.

Measures of Vedolizumab Efficacy and Safety

Corticosteroid dose over time was assessed for each patient in relationship to vedolizumab initiation; we considered 9 mg of budesonide equivalent to 20 mg of prednisone daily. Corticosteroids used solely as part of anti-rejection regimens were not included in the IBD-related corticosteroid assessment, but were recorded separately. Clinical improvement in IBD activity was defined using the gastroenterologist's global assessment of clinical disease activity at 3, 6, and 12 months following vedolizumab initiation as reflected in provider documentation within the medical record. When available, endoscopic response was defined as an improvement of mucosal inflammation on post-treatment endoscopy. Treatment failure was defined as the need for colectomy due to IBD activity, insufficient clinical response by physician global assessment, persistent pulses of systemic corticosteroids following vedolizumab initiation, the development of new fistulizing disease, or transitioning to an alternative treatment. Infections were categorized as bacterial, fungal, or viral based on isolated pathogenic organism.

Results

Patient Characteristics

There were 10 LT recipients with moderate to severe IBD (8 UC and 2 CD) who received vedolizumab therapy between 2014 and 2016 (Table 1). Both patients with CD had undergone a prior ileocolonic resection. Of those with UC, 6 patients had pancolitis, while 2 had left-sided colitis. Three (3) patients were diagnosed with new onset IBD post LT. Four patients had previous exposure to anti-TNF agents, two had received agents prior to liver transplantation and two had received agents after liver transplantation prior to vedolizumab therapy. Vedolizumab was administered by standard induction protocol of 300 mg at weeks 0, 2, and 6 and then every 8 weeks thereafter. Two patients ultimately underwent shortening of vedolizumab infusion interval to every 4 weeks due to ongoing disease activity.

Of note, 3 cirrhotic patients underwent transplant while receiving vedolizumab without interruption. At the time of vedolizumab initiation, all subjects were receiving IBD-related corticosteroids, 8 were receiving aminosalicylates, and 3 were on azathioprine or mycophenolate mofetil to treat IBD. Primary sclerosing cholangitis (PSC) was the most common reason for transplantation (9/10). Three patients (Patients #4,7,9) experienced recurrent PSC prior to vedolizumab start; no patients developed recurrent PSC while using

vedolizumab. One patient was transplanted for Hepatitis C Virus-related cirrhosis and underwent successful eradication with direct acting antiviral therapy prior to vedolizumab. All donor grafts were from deceased donors.

IBD Treatment Outcomes

The median duration of observation while using vedolizumab was 13.1 months (range 6.2–24.5). After 6 and then 12months of treatment, 7/10 and later 6/10 patients on vedolizumab had maintained clinical improvement (Table 2). Treatment failure occurred in four patients: two patients with UC requiring colectomy at 6 and 11 months (Patients #9, 7), one patient with CD who developed new perianal fistulas (Patient #8), and one patient with moderate UC continuing to require prednisone for adequate clinical control (Patient #10). One of the six responders required more frequent vedolizumab dosing (every 4 weeks) to maintain clinical response (Patient #4).

All patients were using IBD-related steroids at vedolizumab initiation. The median daily corticosteroid dose immediately prior to vedolizumab start was 25 mg (range: 20–60 mg). At 6 months following vedolizumab induction, 1/10 patients was receiving <50% original steroid dose, while 4/10 eliminated all IBD-related steroids. At 12 months following induction in patients still using vedolizumab, 3/10 patients were receiving <50% original steroid dose and 3/10 patients eliminated all IBD-related steroids. Only 2/10 patients received steroids for graft-related immunosuppression during any time in the first year after start of vedolizumab, with dose ranging from 5–10mg prednisone daily. Of those patients who continued vedolizumab, 5/8 demonstrated endoscopic improvement at 6–12 months following induction.

Infectious complications pre and post-vedolizumab

During the exposure to vedolizumab, 5 patients experienced a total of 11 infections (4 cholangitis, 4 *Clostridium difficile* colitis, 2 empyema, and 1 pneumonia). This represents a rate of 0.95 infections per person year of vedolizumab exposure. Three of the four cases of cholangitis occurred in patients with pre-existing PTC tubes prior to vedolizumab use. Four episodes of *Clostridium difficile* colitis occurred in two individuals who suffered from *Clostridium difficile* colitis episodes prior to vedolizumab initiation (Patient #3 and #7). Resolution of *Clostridium difficile* diarrhea occurred after treatment with standard 2-week course of oral vancomycin in one case and prolonged oral vancomycin taper in three cases. There were no deaths secondary to any infection but hospitalization requiring intensive care unit monitoring was required in one case of cholangitis. No systemic fungal, viral, or mycobacterial infections occurred during the period of vedolizumab exposure. There was no evidence of HCV reactivation in subject #6 after receiving vedolizumab for 12 months.

Liver Transplant Outcomes

Three cirrhotic patients underwent liver transplantation while receiving maintenance vedolizumab therapy. One patient with UC underwent their first liver transplant for PSC (MELD 22) after 2 months of vedolizumab treatment (Patient #5). His preLT course was complicated by an intrahepatic abscess requiring percutaneous drainage and IV antibiotics 1 month prior to initiation of vedolizumab. Post-operatively he developed an empyema at 30

days that was treated with antibiotics. A second patient with CD underwent his second liver transplant for recurrent PSC (MELD 31) after having been on vedolizumab for 19.3 months (Patient #2). Post-operatively his course was complicated by a bile leak requiring surgical revision of his choledochojejunostomy. Finally, a third patient with UC and PSC (Patient #3) underwent his third LT for anti-TNF therapy related cholestatic liver injury (MELD 35) while receiving vedolizumab for 5 months preLT. Post-operatively his course was complicated by a leak of his hepaticojejunsotmy requiring surgical repair. Each of these patients remains on vedolizumab at the time of writing.

As described in Table 1, 9 of the 10 patients received maintenance tacrolimus-based immunosuppression while receiving vedolizumab. One patient received basiliximab induction at the time of LT (Patient #5); of note this patient was using vedolizumab at the time of LT. All other patients had been given standard doses of tacrolimus, mycophenolate, and corticosteroids per protocol. The daily doses of tacrolimus were stable along with stable blood levels during vedolizumab administration. Of note, liver biochemistry levels were stable in LT recipients receiving vedolizumab and no patients had evidence of rejection during a median postLT follow-up of 13.1 months following first exposure to vedolizumab. In addition, there were no episodes of calcineurin inhibitor related neurotoxicity or nephrotoxicity.

Discussion

Vedolizumab was a safe and effective steroid-sparing therapy for the treatment of moderate to severe IBD among 10 liver transplant recipients seen at a single transplant center over a 2-year period. Clinical improvement was observed in 7/10 and 6/10 patients after 6 and 12 months of therapy respectively. At 12 months, 6/10 patients were able to significantly reduce or discontinue IBD-related corticosteroids. However, we note that 5 patients experienced an infection following vedolizumab initiation. The majority of infections occurred in patients with prior episodes (*Clostridium difficile* and PTC tube-related cholangitis) or in the immediate post-transplant period (empyema). All infections responded to antibiotics and there were no deaths. Furthermore, patients undergoing transplant while using vedolizumab experienced no opprotunisitc fungal, viral or mycobacterial infections. While difficult to definitively confirm, we do not believe any of the observed bacterial infections were the result of vedolizumab use.

The ability to target the intestinal tract using vedolizumab provides an attractive option in LT recipients already receiving anti-rejection immunosuppressive regimens, and may be a uniquely effective therapy in special IBD populations. The principle limitations of this retrospective, single center study is the small sample size, limited duration of follow-up, and unaccounted decision bias. However, patients with liver disease are typically excluded from clinical trials of IBD therapeutics, giving value to observational study. Going forward, prospective registry studies are needed to better understand the long term efficacy and safety of intestine specific treatments in the expanding population of solid organ transplant candidates and recipients.

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Abbreviations

CD	Crohn's disease
UC	Ulcerative colitis
IBD	Inflammatory bowel disease
LT	Liver transplantation
PSC	Primary sclerosing cholangitis
TNF	Tumor necrosis factor

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Table 1

Patient characteristics at the time of vedolizumab initiation

	***N*=10** *
Age at Liver Transplant, years	36 (28.5–50)
Age at Start of Vedolizumab, years	44 (36–53)
Male (%)	8 (80%)
Caucasian (%)	10 (100%)
BMI median, kg/m2	24.6 (17.1–36.8)
Etiology of Liver Disease	
Primary Sclerosing Cholangitis (%)	9 (90%)
Hepatitis C (%)	1 (10%)
Time Post Transplant, years	1.6 (−1.6–14.2)
IBD diagnosis	
Ulcerative Colitis (%)	8 (80%)
Crohn's Disease (%)	2 (20%)
IBD Disease Duration, years	14.5 (1.6–33.7)
IBD diagnosis Relative to OLT	
Pre-OLT (%)	7 (70%)
Post-OLT (%)	3 (30%)
Prior IBD Therapy Exposure	
Thiopurine (%)	4 (40%)
Anti-TNF (%)	4 (40%)
Aminosalicylates (%)	9 (90%)
Duration of Vedolizumab Use, months	13.1 (6.2–24.5)
Lab parameters	
Creatinine (mg/dL)	0.9 (0.6–1.2)
Hemoglobin (g/dL)	12.1 (9.4–15.4)
Total Bilirubin (mg/dL)	0.8 (0.3–36.1)
ALT (IU/L)	25 (11–100)
Anti-HBc (+) (%)	1 (10%)
Quantiferon TB Test Status	
Positive (%)	0 (0%)
Indeterminate (%)	3 (30%)
Negative (%)	7 (70%)

* Data reported as Median (range) or n(%)

Table 2

Individual LT recipients and outcomes following vedolizumab initiation

Patient	Primary Liver Disease	CMV Status (D/R)	Vedo Start Post-OLT (years)	Calcineurin Inhibitor	IBD Type	Prior Biologic	Thiopurine Use	Pre-Vedo Steroids (mg)	Pre-Vedo Endoscopy	6 Month Outcome	12 Month Outcome	Vedo Duration (months)
1	PSC	−/+	14.2	Tacrolimus 1mg BID	UC		No	50 *	Severe	Resp.	Resp.	12.1
2	PSC #@	−/−	−1.6	Cyclosporin 125mg BID	CD	IFX, ADA	Yes	20 *	Moderate	Resp.	Resp.	24.5
3	PSC #	−/+	−0.4	Tacrolimus 3mg BID	UC	ADA	No	20	Severe	Resp.	Resp.	22.2
4	PSC	−/+	11.3	Tacrolimus 2mg BID	UC		No	20	Moderate	Resp.	Resp.	16.1
5	PSC #	−/+	−0.2	Tacrolimus 4mg BID	UC		No	20 *	Severe	Resp.	Resp.	14.1
6	HCV	+/+	3.2	Tacrolimus 3mg/2mg BID	UC		No	30	Moderate	Resp.	Resp.	12.6
7	PSC	−/−	1.7	Tacrolimus 3mg BID	UC	IFX	No	20 *	Severe	NR–> Add AZA	Fail, Colectomy	13.6
8	PSC	−/−	1.5	Tacrolimus 2mg BID	CD	IFX, ADA	Yes	40	Moderate	NR–> Inc. AZA	Fail, Alt therapy	11.0
9	PSC	−/−	15.5	Tacrolimus 4mg BID	UC		Yes	30 *	Severe	Fail, Colectomy	N/A	6.2
10	PSC	−/−	0.3	Tacrolimus 3mg/4mg BID	UC		Yes	30 *	Moderate	Resp.	Fail, Steroid pulses	6.2

Abbreviations: PSC, primary sclerosing cholangitis; HCV, hepatitis c virus; UC, ulcerative colitis; CD, Crohn's disease; IFX, infliximab; ADA, adalimumab; Vedo, vedolizumab; Resp., Responder; NR, Non-responder; AZA, azathioprine; CMV, cytomegalovirus; D/R, donor/receipient.

Liver transplantation without vedolizumab interruption

@ Liver and kidney transplantation

* Corticosteroid dose calculation included budesonide.