Title:
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Efficacy and safety of vedolizumab as a treatment option for moderate to severe refractory ulcerative colitis in two patients after liver transplant due to primary sclerosing cholangitis

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ABSTRACT

Vedolizumab is a humanized IgG1 monoclonal antibody that selectively blocks the lymphocyte integrin α4β7 and prevents its interaction with endothelial adhesion molecules and subsequent transmigration to the gastrointestinal tract. The drug was approved in 2014 for the induction and maintenance treatment of ulcerative colitis and moderate to severe Crohn’s disease that is refractory or intolerant to conventional treatment with corticoids and immunosuppressants and/or anti-TNFα drugs. However, inflammatory bowel disease has a variable behavior following liver transplant. One third of patients with ulcerative colitis associated with primary sclerosing cholangitis are expected to deteriorate despite receiving immunosuppression to prevent rejection. There is limited experience with anti-TNFα agents in patients with inflammatory bowel disease in the setting of liver transplantation and the studies to date involve a limited number of cases. The efficacy and safety data of vedolizumab in
this situation are unreliable and very preliminary. We present two cases with the aim to present the efficacy and safety of vedolizumab after one year of treatment in two patients who underwent a transplant due to primary sclerosing cholangitis. One case had de novo post-transplant ulcerative colitis refractory to two anti-TNFα drugs (golimumab and infliximab). The other patient had a colostomy due to fulminant colitis and developed severe ulcerative proctitis refractory to infliximab after reconstruction with an ileorectal anastomosis.

**Key words:** Vedolizumab. Liver transplant. Ulcerative colitis.

**INTRODUCTION**

Vedolizumab is a humanized IgG1 monoclonal antibody that selectively blocks the lymphocyte integrin α4β7 and is a recent addition to the widened therapeutic arsenal for the treatment of moderate to severe inflammatory bowel disease (IBD) (1,2). Due to its selective action in the digestive tract, it has potential advantages in certain patient profiles (high risk of infection or tumor) such as transplant patients. Around 5% of patients with IBD are estimated to develop primary sclerosing cholangitis (PSC), a chronic fibro-inflammatory disorder with currently no effective treatment. This disease results in end-stage liver disease and the need for a liver transplant (3). Post-transplant immunosuppression does not prevent the de novo onset of IBD or the worsening of the pre-existing disease. Anti-TNFα agents are the treatment standard for moderate to severe IBD refractory to treatment with corticoids and immunosuppressants. However, there are serious concerns among physicians with regard to their use in a patient who is already immunosuppressed due to a transplant. In addition, data with regard to the efficacy and safety of anti-TNFα agents in this situation are very limited, although they are apparently similar to those of non-transplanted patients with IBD. The aim of reporting these two cases is to add further information to the limited everyday experience reported with regard to the use of vedolizumab in ulcerative colitis refractory to conventional management in the context of liver transplant patients.

**CASE REPORT 1**
A 35-year-old woman with no toxic habits or relevant family history was diagnosed with PSC in 2010. After diagnosis, she underwent screening for ulcerative colitis via a complete lower digestive endoscopy and no macroscopic or histological changes were found. In 2013, she received a deceased donor liver transplant due to hepatocellular insufficiency and repeated cholangitis. She experienced no immediate post-transplant complications, had good graft function and was on a prolonged-release tacrolimus-based immunosuppression regimen.

Nine months after the transplant the patient started to have bloody diarrhea which was diagnosed as extensive ulcerative colitis with moderate clinical and endoscopic activity. After the initial diagnosis, the patient satisfied the criteria for corticosteroid-dependent ulcerative colitis. The use of azathioprine was discarded as the patient had discrete leucopenia. Thus, she was treated with the biological anti-TNFα drug, golimumab, subcutaneously (usual induction dose of 200 mg sc initially and 100 mg at two weeks) and a 50 mg monthly maintenance (patient weight 61 kg).

The patient required intensification to 100 mg monthly from the second treatment month as the response to golimumab was only partial. However, four months after starting golimumab this treatment was changed to an intravenous anti-TNF drug (infliximab) because the patient could not be weaned from the oral corticosteroids. Nevertheless, after starting infliximab at the conventional induction dose (5 mg/kg IV, weeks 0, 2 and 6) no clinical response was achieved. In addition, it was not possible to withdraw the corticosteroids after six months of treatment despite early intensification from the fifth infusion (5 mg/kg IV every four weeks). Infliximab levels in blood were in the therapeutic range. This, together with the absence of anti-infliximab antibodies and a concomitant enteric infection or superinfection with cytomegalovirus, led to a change in the therapeutic target.

In December 2016 (35 months post-transplant), treatment was started with vedolizumab following the usual induction regimen (300 mg IV on weeks 0, 2 and 6) and maintenance with 300 mg vedolizumab IV every eight weeks. The patient had a total Mayo score of 7 immediately before starting vedolizumab. After the second infusion, she experienced a clinical response with normalization of stool habit but continued to have elevated biological activity parameters (fecal calprotectin: 805
mcg/g, C-reactive protein [CRP]: 8 mg/dl). Corticosteroids were withdrawn three months after starting vedolizumab.

Vedolizumab treatment was intensified one month later by shortening the interval of infusions to four weeks. One year after starting treatment, the total Mayo score was 4 (endoscopic subscore 1), the calprotectin had fallen to 270 mcg/g and the CRP levels had normalized. Tacrolimus concentrations remained stable within the desired range (5-10 ng/ml) and there was no need for dose adjustment. The liver biochemistry results remained stable throughout this period. There have been no infectious adverse events or pharmacological interactions to date.

CASE REPORT 2

A 37-year-old woman with no toxic habits or relevant family history was diagnosed with PSC in 2008 and extensive ulcerative colitis one year later. During the first two years, the ulcerative colitis presented mild activity and was treated with oral mesalazine.

Towards the end of 2010, the patient experienced increased inflammatory activity and developed criteria for corticosteroid dependence, requiring biological treatment with infliximab. Clinical and biological remission was achieved after treatment. The patient experienced a deterioration of the ulcerative colitis concomitantly with a rapid decompensation of the PSC and was prioritized for orthotopic liver transplant due to severe hepatocellular insufficiency and complications from the portal hypertension. The patient underwent a deceased-donor liver transplant in March 2011 (withdrawal of infliximab one month before transplantation), and received immunosuppression with a delayed-release tacrolimus regimen.

She presented severe acute cellular rejection as an immediate postoperative complication and required complete steroid recycling. The ulcerative colitis remained stable and was treated with oral and topical mesalazine until January 2012 (eleven months after transplantation). At this time she experienced an increase in the clinical and biological activity and restarted biological anti-TNFα treatment with infliximab following the usual induction regimen (5 mg/kg on weeks 0, 2 and 6) with maintenance treatment every eight weeks. The dose was intensified after two months (shortening
of infusions to every six weeks) as the clinical response was not complete. In March 2012, the patient had a cytomegalovirus infection which was successfully treated with oral valganciclovir. Two months later, infliximab was changed to adalimumab sc (180:60 and 40 mg each two weeks) due to a severe infusion reaction. The patient failed to respond to adalimumab and experienced a severe flare-up in September 2012 that required a total colectomy with preservation of the rectal stump and ileostomy. One month later, the tract was reconstructed via an ileorectal anastomosis due to the wishes of the patient. She was given exhaustive information about the advantages and disadvantages related to reservoir co-infection with an ileoanal anastomosis.

After restoring transit, the patient developed refractory inflammation of the rectal stump (total Mayo score 8, calprotectin 708 mcg/gr, CRP 9.5 mg/l) with incapacitating diarrhea that did not respond to treatment with oral and topical mesalazine. The patient was also dependent on high doses of oral steroids in order to control symptoms.

In January 2016 she was treated with vedolizumab (300 mg IV in weeks 0, 2 and 6, and then every eight weeks) due to the previous infusion reaction with infliximab and the lack of previous efficacy with adalimumab. A clinical response was induced, and clinical remission and improvement in the biological parameters (reduction in calprotectin to 192 mcg/gr and normalization of CRP) and the endoscopic subscore (Mayo 1; previous 3) were achieved 12 months after starting treatment without shortening the interval of vedolizumab. No adverse effects attributable to vedolizumab or interactions with tacrolimus affecting immunosuppression levels were observed.

**DISCUSSION**

The therapeutic management of IBD after liver transplant can be a real clinical challenge. It is estimated that the IBD (mainly ulcerative colitis) will deteriorate in 30% of patients who receive a transplant due to PSC diagnosed after IBD, requiring intensification of the medical treatment and/or surgery. In addition, about 21% of patients transplanted due to PSC will develop de novo IBD within four years of the transplant (4). The current treatment paradigm for moderate to severe IBD is
immunosuppressants, with or without biological anti-TNF agents. Vedolizumab has been recently incorporated into the arsenal of therapeutic options for patients with moderate to severe IBD that is intolerant or refractory to treatment directed against the tumor necrosis factor.

The experience with biological anti-TNFα agents after liver transplant is limited and the published case series include only a few patients (5,6). With regard to the use of vedolizumab, there are only 12 cases reported so far, in two case reports (7,8) and two case series. The first case series included five patients who all received a liver transplant due to PSC and presented stage E3 ulcerative colitis. The ulcerative colitis was diagnosed de novo after the transplant in two patients. Four patients received tacrolimus-based immunosuppression therapy and four patients had prior exposure to anti-TNFα agents. All patients received maintenance therapy as they all showed a clinical response. No adverse effects were noted during a mean follow-up period of eight months (9).

In the second series, which was comprised of five patients, one of the cases presented ileocolonic Crohn’s disease. The other cases all had Montreal stage E3 ulcerative colitis. As in the first series, two patients were diagnosed de novo post-transplantation. Tacrolimus was used as an anti-rejection therapy in all the patients, with two also receiving mycophenolate mofetil. Two patients had prior exposure to anti-TNFα agents (one golimumab and the other infliximab). One patient had a colectomy prior to vedolizumab treatment. The overall clinical response was 60% (two in clinical remission with mucous healing 14 weeks after starting treatment). The two non-responders had a colectomy. No adverse effects attributable to vedolizumab were recorded during a mean follow-up of 6.8 months (10). Table 1 summarizes the demographic characteristics and the efficacy and safety data for the 12 cases reported to date.

Aside from a few peculiarities, the two cases reported here are typical of those reported so far in the literature. The first patient was diagnosed with de novo ulcerative colitis in the context of a liver transplant due to PSC. This is not very common as less than half of patients develop ulcerative colitis post-transplant. The second patient had to undergo a colectomy beforehand and was subsequently
diagnosed with a severe refractory proctitis. The usual clinical scenario is refractoriness prior to anti-TNF treatment (two agents used in the first patient) and tacrolimus-based immunosuppression. As previously reported, no adverse effects related to vedolizumab were noted during the follow-up of almost one year, nor were there interactions with the immunosuppressive treatment for the transplanted organ.

The high specificity of vedolizumab for the digestive tract that selectively blocks the interaction between the integrin α4β7 and the endothelial adhesion molecule MadCAM-1 results in the interruption of lymphocyte transmigration to the submucosa of the gastrointestinal tract. This results in an inhibition of the local inflammatory response without affecting the systemic immune vigilance. This is of particular relevance in the context of a liver transplant, as the inevitable immunosuppression to prevent rejection multiplies the chances of severe adverse events. One disadvantage of this approach is the risk of colorectal cancer. The association of PSC plus ulcerative colitis results in an increased risk of colorectal cancer. A weakened local immune vigilance by the selective mechanism of action of vedolizumab is a particular concern in this context. Long-term real life studies may enable this issue to be resolved.

The specific situation of ulcerative colitis in patients with PSC has certain implications that have aroused great interest of late. MadCAM-1 is normally expressed in the vessels in the lining of the digestive tract where it is involved in the recruitment of lymphocytes expressing α4β7. In the context of PSC, MadCAM-1 expression is also detected in the hepatic endothelium, encouraging the recruitment of α4β7 effector lymphocytes from the digestive tract. Thus, vedolizumab and other therapies that act on the α4β7-MadCAM-1 interaction are promising drugs for the treatment of PSC.

Preliminary data suggest that vedolizumab appears to be an efficient option for patients with moderate to severe IBD that is also refractory to biological treatment. This treatment also has a favorable safety profile, although more cases and long term follow-up in transplant patients are required.

REFERENCES


Table 1. Baseline and treatment-related characteristics of patients treated with vedolizumab for inflammatory bowel disease after liver transplant

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F: Female; M: Male; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis; UC Ext: Extensive ulcerative colitis; CD: Crohn’s disease; CD Ileoc: Ileocolonic Crohn’s disease; SCCAI: Simple clinical colitis activity index; TMS: Total Mayo score; HBi: Harvey Bradshaw index; Tac: Tacrolimus; AZA: Azathioprine; Pred: Prednisone; MMF: Mycophenolate mofetil; IFX: Infliximab; Gol: Golimumab; VDZ: Vedolizumab; Colec: Colectomy; NA: Not available; LT: Liver transplant. *The number in parentheses refers to the literature reference of the patient.