CASE REPORT

Evolving strategies to reduce colectomy rates in primary sclerosing cholangitis-inflammatory bowel disease: clinical remission of corticosteroid refractory colitis post-liver transplant with vedolizumab

Saqib Mumtaz,¹ Jason Goh,¹ Gideon M Hirschfield,^{2,3} James Ferguson,³ Sheldon C Cooper¹

¹Department of Gastroenterology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

²NIHR Liver Biomedical Research Unit, University of Birmingham, Birmingham, UK

³Liver Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Correspondence to

Dr Saqib Mumtaz, Department of Gastroenterology, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B152GW, UK; drsaqibmumtaz@gmail.com

Published Online First
5 August 2016

ABSTRACT

Primary sclerosing cholangitis (PSC) is associated with inflammatory bowel disease (IBD) in approximately 70% of patients, with ulcerative colitis (UC) being the most common subtype of IBD identified. There is a paucity of data on the optimum management strategy for IBD flares in the post-liver transplant patient, particularly when refractory to conventional treatments. Vedolizumab is a novel gut-specific monoclonal antibody, which has recently been approved for use by National Institute for Health and Care Excellence for moderate-to-severe UC. We present an exemplar case of successful use of vedolizumab in the management of corticosteroid refractory PSC-IBD after liver transplantation.

The clinical course of primary sclerosing cholangitis-inflammatory bowel disease (PSC-IBD) is clinically recognised to pursue a distinct course, one feature of which is troublesome colitis post-liver transplantation despite adequate immunosuppression. We report the case of a previously healthy 22-year-old female, who initially presented to her general practitioner (GP) with symptoms of lethargy, weight loss and pruritus. She was found to have abnormal liver biochemistry tests and subsequent investigations confirmed a diagnosis of advanced cirrhotic PSC. Although she did not have any bowel symptoms, a screening colonoscopy revealed endoscopic and

histologic features of pancolitis (Mayo Endoscopy Score (MES) of 1)¹ and she was commenced on a maintenance dose of mesalazine 800 mg twice a day.

In the ensuing months, her liver synthetic function deteriorated rapidly (bilirubin 297 µmol/L, albumin 33 g/L, international normalised ratio 1.3) and within 3 months of the diagnosis of PSC, she was listed for liver transplantation. She successfully underwent an orthotopic liver transplant (OLT) with an uncomplicated discharge a week later on standard triple immunosuppressives (tacrolimus, azathioprine and tapering prednisolone) and her usual mesalazine.

Seven months post-transplant, the patient presented with a mild flare of her IBD, passing loose stools, accompanied with occasional blood per rectum and abdominal pain. She was on tacrolimus and low-dose prednisolone for immunosuppression. Azathioprine had been stopped due to neutropenia. The first step was to cautiously increase her prednisolone dose to 20 mg once a day and mesalazine to 2.4 g/day. This failed to improve her condition and by the end of the month she was passing more than 10 bloody stools per day and developed iron deficiency anaemia (haemoglobin 76 g/L) with a Simple Clinical Colitis Activity Index (SCCAI) score of 10.² She was admitted to the hospital for intravenous

CrossMark

To cite: Mumtaz S, Goh J, Hirschfield GM, et al. *Frontline Gastroenterology* 2016;7:271–274.

Figure 1 Photograph showing the sigmoid colon pre-vedolizumab.

Figure 2 CT scan of the abdomen showing pancolitis.

hydrocortisone and iron infusion. Flexible sigmoidoscopy revealed normal rectum but active colitis to the extent of examination (figure 1) with a MES of 2. CT scan of the abdomen confirmed an active pancolitis (figure 2). Histology of the sigmoid colon biopsies was negative for *Cytomegalovirus* (CMV) by immunohistochemistry, but serology indicated mild CMV viraemia (853 copies/mL). She was treated with oral valganciclovir. Azathioprine was now reinstated at a lower dose and mesalazine was optimised to 2.4 g twice a day. Her condition improved with 5 days of intravenous corticosteroids and she was discharged on a reducing dose of prednisolone 40 mg once a day.

Unfortunately her symptoms quickly recurred, with bloody diarrhoea, including nocturnally and significant weight loss. The option of colectomy was discussed with the patient but she found this difficult to accept so soon after her liver transplant. Rescue therapy in the form of anti-tumour necrosis factor

(anti-TNF) monoclonal antibody was deemed inappropriate in the setting of triple immunosuppression and recent CMV viraemia.

National Institute for Health and Care Excellence had approved vedolizumab for management of moderate-to-severe ulcerative colitis (UC). Although there are no specific recommendations for management of PSC-IBD, especially post-liver transplant, but there were good data to suggest that vedolizumab would be an appropriate choice in patients with PSC-IBD. After multi-disciplinary team discussion, it was decided to offer the patient a trial of vedolizumab.

The first infusion of vedolizumab 300 mg was given as an inpatient, followed by two further induction doses as outpatient at weeks 2 and 6, respectively. The patient's symptoms improved after the first dose with clinical remission by the third dose (SCCAI score 2). Follow-up colonoscopy post third dose, confirmed mucosal healing with MES 0 (figure 3). Eight months post the first dose of vedolizumab, the patient remained in clinical remission, continuing with maintenance infusion every 8 weeks.

DISCUSSION

PSC is associated with IBD in approximately 70% of patients, with UC being the most common subtype of IBD identified (>75%).^{3 4} In fact PSC-IBD represents a unique phenotype characterised by rectal sparing, high prevalence of pancolitis, backwash ileitis, mild histological inflammation and usually a mild or quiescent clinical course.⁵⁻⁷ The natural history of IBD after liver transplant for PSC is very variable. In a clinical review of 14 observational studies, Singh *et al*⁸ conclude that 31% of patients experience an improvement in their IBD activity compared with their pre-OLT course, whereas 39% of patients have no

Figure 3 Photograph showing the sigmoid colon post-vedolizumab.

significant change. Interestingly, one-third of patients may paradoxically worsen despite the transplant immunosuppression regime. There is a paucity of data on the optimum management strategy for flare of IBD post-OLT, which is refractory to conventional treatments. There is limited experience regarding the long-term efficacy and safety of anti-TNF therapy in patients with OLT who are on concurrent immunosuppression. The two largest case series on the use of anti-TNF agents for management of IBD after OLT include six and eight patients, respectively.^{9 10} In these retrospective studies, clinical response, based on physician's global assessment, was seen in 11 out of 14 patients (78.5%). However, use of these agents was associated with significant side effects, including serious infections, recurrent PSC and lupus. One patient was diagnosed with colorectal cancer 9 months after the use of anti-TNF therapy and another with post-transplant lymphoproliferative disorder after 4 months of anti-TNF use. For most patients, surgery is the eventual outcome. Proctocolectomy with ileal pouch anal anastomosis or end-ileostomy is feasible and safe after OLT, with good results.^{11–13} Although surgery removes the need for annual colonoscopies, its role in recurrence of PSC in the graft liver is unclear.^{14 15} There is also a reported risk of 14%–66% of acute pouchitis and 9%–74% of chronic pouchitis after OLT for PSC.^{11 12 16}

We present an exemplar case of vedolizumab for management of IBD after a liver transplant for PSC. Vedolizumab is a highly specific humanised monoclonal antibody that exclusively targets the gut-tropic $\alpha_4\beta_7$ integrin, selectively antagonising the interaction between $\alpha_4\beta_7$ and mucosal addressin cell adhesion molecule-1 (MAdCAM 1) and binding to fibronectin.^{17–19} The end effect is prevention of lymphocyte transmigration into the gut submucosa, with the potential to inhibit local inflammatory responses, without impairing systemic immunosurveillance.¹⁸ The gut-specific nature of vedolizumab prompted consideration of use in this patient, potentially preventing the adverse events of systemic over-immunosuppression.

Vedolizumab presents a new prospect for medical treatment of colitis in patients with PSC both in the pre-transplant and post-transplant settings. In fact there is interest among the PSC experts regarding its role in the management of PSC. MAdCAM-1 is known to be expressed on the intestinal mucosal vessels where it is involved in the recruitment of lymphocyte expressing integrin $\alpha_4\beta_7$. Normally this endothelial adhesion molecule displays a restricted expression pattern confined to the gut. However in PSC liver, MAdCAM-1 is also detected on hepatic endothelial cells and supports the recruitment of gut tropic $\alpha_4\beta_7$ effector lymphocytes.^{20 21} Hence therapies targeting $\alpha_4\beta_7$ -MAdCAM-1 interactions in

hepatobiliary inflammation represent potential for future treatments in PSC.²²

Although long-term data are lacking, our experience, along with evolving data from other centres,²³ is promising and suggests an opportunity to further evaluate the clinical impact of vedolizumab in PSC-IBD. Given the enhanced risk of colorectal cancer in PSC-IBD, it will however be important to ensure post-marketing registry data are maintained to help inform risk-benefit evaluations.

In conclusion we present the successful use of vedolizumab in a patient post-liver transplant with a corticosteroid refractory flare of colitis.

Acknowledgements Melanie Love, IBD Nurse Specialist, Queen Elizabeth Hospital.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;317:1625–9.
- Walmsley RS, Ayres RC, Pounder RE, *et al.* A simple clinical colitis activity index. *Gut* 1998;43:29–32.
- Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012;56:1181–8.
- Olsson R, Danielsson A, Järnerot G, *et al.* Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991;100(Pt 1):1319–23.
- Loftus EV Jr, Harewood GC, Loftus CG, *et al.* PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut* 2005;54:91–6.
- Boonstra K, van Erpecum KJ, van Nieuwkerk KM, *et al.* Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2270–6.
- O'Toole A, Alakkari A, Keegan D, *et al.* Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. *Clin Gastroenterol* 2012;10:439–41.
- Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. *Am J Gastroenterol* 2013;108:1417–25.
- Sandhu A, Alameel T, Dale CH, *et al.* The safety and efficacy of antitumour necrosis factor- α therapy for inflammatory bowel disease in patients post liver transplantation: a case series. *Aliment Pharmacol Ther* 2012;36:159–65.
- Mohabbat AB, Sandborn WJ, Loftus EV Jr, *et al.* Anti-tumour necrosis factor treatment of inflammatory bowel disease in liver transplant recipients. *Aliment Pharmacol Ther* 2012;36:569–74.
- Cho CS, Dayton MT, Thompson JS, *et al.* Proctocolectomy-ileal pouch-anal anastomosis for ulcerative colitis after liver transplantation for primary sclerosing cholangitis: a multi-institutional analysis. *J Gastrointest Surg* 2008;12:1221–6.
- Mathis KL, Dozois EJ, Larson DW, *et al.* Ileal pouch-anal anastomosis and liver transplantation for ulcerative colitis complicated by primary sclerosing cholangitis. *Br J Surg* 2008;95:882–6.

- 13 Bosso MC, Marchesa PE, Ricchiuti A, *et al.* Proctocolectomy for ulcerative colitis after liver transplantation for primary sclerosing cholangitis. *Transplant Proc* 2009;41:1390–2.
- 14 Alexander J, Lord JD, Yeh MM, *et al.* Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 2008;14:245–51.
- 15 Campsen J, Zimmerman MA, Trotter JF, *et al.* Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. *Liver Transpl* 2008;14:181–5.
- 16 Zins BJ, Sandborn WJ, Penna CR, *et al.* Pouchitis disease course after orthotopic liver transplantation in patients with primary sclerosing cholangitis and an ileal pouch-anal anastomosis. *Am J Gastroenterol* 1995;90:2177–81.
- 17 Fedyk ER, Wyant T, Yang LL, *et al.* Exclusive antagonism of the $\alpha 4 \beta 7$ integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis* 2012;18:2107–19.
- 18 Haanstra KG, Hofman SO, Lopes Estêvão DM, *et al.* Antagonizing the $\alpha 4 \beta 1$ integrin, but not $\alpha 4 \beta 7$, inhibits leukocytic infiltration of the central nervous system in rhesus monkey experimental autoimmune encephalomyelitis. *J Immunol* 2013;190:1961–73.
- 19 Soler D, Chapman T, Yang LL, *et al.* The binding specificity and selective antagonism of vedolizumab, an anti- $\alpha 4 \beta 7$ integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther* 2009;330:864–75.
- 20 Trevidi PJ, Adams DH. Mucosal immunity in liver autoimmunity: a comprehensive review. *J Autoimmun* 2013;46:97–111.
- 21 Trevidi PJ, Adams DH. Gut-liver immunity. *J Hepatol* 2016;64:1187–9.
- 22 Trevidi PJ, Hirschfield GM. Treatment of Autoimmune liver disease: current and future therapeutic options. *Ther Adv Chronic Dis* 2013;4:119–41.
- 23 Meszaros M, Pageaux GP, Altwegg R. Management of ulcerative colitis using Vedolizumab after liver transplantation for Primary Sclerosing Cholangitis. *J Crohns Colitis* 2016;10:236.