

Safety and Efficacy of Biologic Agents for the Management of Inflammatory Bowel Disease After Liver Transplantation

Suhail A. Shaikh, Linda Fitzgerald, and Sarah Tischer*

Department of Pharmacy Services and Clinical Sciences, University of Michigan Health System, Ann Arbor, Michigan

Primary sclerosing cholangitis (PSC) frequently progresses to end-stage liver disease and cirrhosis, requiring liver transplantation. Approximately 70% of patients with PSC have concomitant inflammatory bowel disease (IBD) during their clinical course. After liver transplantation for PSC, corticosteroids and other high-intensity immunosuppressants are initiated to keep IBD in remission. Patients with IBD that is refractory to these agents may need to be managed with biologic therapies. Biologic agents, however, may further increase the risks for malignancy and infection due to their immunosuppressive effects. Thus, to gain a better understanding of the risks and benefits of these agents in this high-risk patient population, we performed a literature search of the PubMed database (2002–2017) to identify studies assessing the efficacy and safety of various biologic agents for the management of IBD in liver transplant recipients. No randomized controlled studies or retrospective comparative studies were identified; however, 15 case reports and case series were identified that met our inclusion criteria. From these case reports, we identified 67 patients who developed de novo or recurrent IBD after liver transplantation and received anti-tumor necrosis factor- α or anti-integrin therapy. Of the 13 published cases reporting clinical response or remission of IBD activity in liver transplant recipients (59 patients), clinical response or remission of IBD was reported in 38 (64.4%) of those patients. Adverse complications reported included cholangitis, oral candidiasis, *Clostridium difficile* colitis, bacterial pneumonia, cryptosporidiosis, Epstein-Barr virus-positive posttransplantation lymphoproliferative disease, and hepatotoxicity. Given the limited literature (case reports and case series) highlighted in this review, biologic agents such as tumor necrosis factor- α inhibitors and integrin inhibitors commonly used for moderate to severe IBD may be appropriate after liver transplantation; however, consideration of risk versus benefit should always occur in a patient-specific manner.

KEY WORDS inflammatory bowel disease, liver transplantation, biologics.

(Pharmacotherapy 2017;37(12):1578–1585) doi: 10.1002/phar.2036

Primary sclerosing cholangitis (PSC) is a rare occurrence among the general population, with

an incidence rate of 0.77 per 100,000 person-years, and it most commonly occurs in middle-aged men.^{1, 2} This chronic cholestatic disease of the liver and bile ducts, characterized by fibrosis of the intrahepatic and extrahepatic bile ducts, frequently progresses to end-stage liver disease and cirrhosis, requiring liver transplantation.

Although the pathogenesis of PSC is not completely understood, it is theorized that PSC is the result of an autoimmune process given its tight association with inflammatory bowel disease (IBD). Approximately 70% of patients with

No funding was required to support the production of this manuscript.

Suhail A. Shaikh, Linda Fitzgerald, and Sarah Tischer declare they have no conflict of interest.

*Address for correspondence: Sarah Tischer, Department of Pharmacy Services and Clinical Sciences, University of Michigan Health System, 1111 E. Catherine St., Ann Arbor, MI 48104; e-mail: tissarah@med.umich.edu.

© 2017 Pharmacotherapy Publications, Inc.

PSC have concomitant IBD during their clinical course, with ulcerative colitis (UC) predominating.² The traditional view of the pathogenesis of IBD is that intestinal inflammation is mediated by infiltration of leukocytes in intestinal mucosa and derangements in intestinal barrier function. During IBD, intestinal inflammation is mediated by cells of the acquired immune system, with overly aggressive activity of effector lymphocytes and proinflammatory cytokines (tumor necrosis factor [TNF]) contributing to the symptoms seen in Crohn's disease and UC.³ After liver transplantation for PSC, corticosteroids are initiated, as well as other high-intensity immunosuppressants, that may keep IBD in remission. However, despite immunosuppression, there is evidence demonstrating both recurrence of IBD or de novo IBD in liver transplant recipients.⁴ Significant risk factors for IBD recurrence and de novo IBD after liver transplantation include IBD before orthotopic liver transplantation (OLT), use of tacrolimus, cytomegalovirus mismatch status, IBD symptoms at time of OLT, and short time interval between diagnosis of IBD and OLT.⁴

Patients with corticosteroid- or immunomodulatory therapy-refractory IBD may need to be managed with biologic therapies, including antibody products acting against TNF- α and integrin. In a patient population already at high risk for malignancy and infection, biologic agents may further increase these risks given their immunosuppressive effects. Therefore, it becomes important to assess the safety and efficacy of these agents in patients with IBD after liver transplantation. Unfortunately, to our knowledge, no randomized controlled studies or retrospective comparative studies were identified to assess the safety and efficacy of these agents for IBD after liver transplantation. However, several case reports and case series were identified to help explore the use of these agents in this patient population, which is the focus of this review.

Background

Association Between PSC and IBD

Several theories exist to describe the association between PSC and IBD, linking PSC to an autoimmune pathophysiology. A study was conducted to investigate whether clonally related T cells were present in paired tumor-adjacent normal gut and liver tissue sampled from patients

with colon cancer.⁵ The study was able to demonstrate that memory T cells of common clonal origin were detected in paired gut and liver samples in patients with PSC and IBD concomitantly (PSC-IBD). These T cells react to similar triggers and are proportionally high in patients with PSC-IBD. To further link PSC to an immunogenic mechanism, immunogenicity studies have identified a number of key human leukocyte antigen (HLA) haplotypes associated with PSC. Specifically, the haplotype HLA-B8/DR3 has been implicated in patients with PSC-IBD and is infrequent in patients with PSC alone.⁶

The clinical presentation and prognosis of PSC and IBD are also similar owing to the association between the two. Patients with PSC-IBD have an increased incidence of pancolitis, rectal-sparing disease, backwash ileitis, and milder symptoms.⁷ Moreover, both PSC and IBD are associated with colorectal cancer, with an increased risk in patients with PSC-IBD likely due to an accumulation of secondary bile acids causing DNA damage and promoting cell mutation.⁸ Given that patients with PSC-IBD have much milder symptoms of IBD, it can often go unrecognized and untreated, which may also increase the risk of colorectal cancer, as extent and duration of colitis are known risk factors for malignancy.⁸ IBD after liver transplantation has severe consequences, including increased risk for graft rejection and need for retransplantation.⁹ Therefore, it is important to recognize those patients at risk for de novo or recurrent IBD after liver transplantation and optimize management to control IBD activity.

Management of PSC

There are a limited number of treatment options for PSC that may be used before liver transplantation such as ursodeoxycholic acid, endoscopic therapy, and biliary surgery. These treatment modalities have not been shown to slow down the progression of PSC but certainly have been shown to have other benefits. Ursodeoxycholic acid has been the only pharmacologic therapy to demonstrate a positive effect for PSC by improving biochemistry, histology, and symptoms, as well as decreasing the incidence of colorectal cancer and cholangiocarcinoma.¹⁰ However, the only treatment option for PSC leading to end-stage liver disease is liver transplantation.¹⁰ Patients who undergo liver transplantation for PSC are at an increased risk

for recurrence of IBD or the development of de novo IBD due to inappropriate and ongoing activation of the mucosal immune system. Furthermore, after liver transplantation, patients receive immunosuppressive medications that may lead to infections affecting the microbial flora, which, in turn, may result in a decrease in intestinal barrier function.

Management of IBD After Liver Transplantation

Management of IBD after liver transplantation has not been well established, with recommendations to use cyclosporine instead of tacrolimus for maintenance immunosuppression, avoid mycophenolate mofetil to minimize the risk of enterocolitis, and use biologic agents for refractory cases of IBD.¹¹ However, the evidence supporting these recommendations is based on small retrospective cohort studies with conflicting data. In patients with refractory or moderate to severe IBD, biologic agents are often required to minimize and maintain IBD activity. Currently, six biologic agents have been approved by the United States Food and Drug Administration (FDA) for IBD, which include inhibitors of TNF- α and integrin.

TNF- α -Based Therapies

TNF- α , a proinflammatory cytokine, is produced by activated macrophages and T-lymphocytes, and proceeds to recruit neutrophils to local sites of inflammation. As demonstrated in randomized controlled trials, neutralizing TNF- α with biologic agents allows for disease remission in patients with IBD.^{12–15} Therefore, these monoclonal antibodies have become the pharmacologic agents of choice for the management of moderate to severe IBD.

Four FDA-approved TNF- α inhibitors are currently available for the treatment of IBD: infliximab, adalimumab, certolizumab, and golimumab. These various TNF- α inhibitors slightly differ in the source (e.g., mouse, human) used to develop the antibody; however, this does not alter the efficacy and safety profiles among the products. Several studies report safety concerns with TNF- α inhibitors including hepatotoxicity, infectious risks, and malignancy.^{12–15}

Integrin-Based Therapies

Integrins are involved in multiple pathways that lead to the development of IBD and

therefore have become a newly targeted area of interest for drug development. Integrins are heterodimers composed of α and β subunits that undergo conformational changes in the response to signaling events inside the cell and function as adhesion receptors that connect cells to ligands in the extracellular matrix to other cells.¹⁶ Lymphocytes play a crucial role in the pathogenesis of IBD, and their journey from the vascular space into the gut tissue is regulated by adhesion molecules and requires multiple steps. The first step in the journey of a leukocyte from circulation into tissue is an interaction with postcapillary vessel endothelium. This process is facilitated by an adhesion system consisting of tethering, rolling, firm adhesion, spreading, and migration of lymphocytes from the vascular space into inflamed tissue.¹⁷

As secondary adhesion molecules, integrins function to stop the rolling lymphocytes and allow migration into intestinal tissue. Several integrin subunits are involved in lymphocyte migration, including $\alpha 2\beta 2$, $\alpha 4\beta 1$, and $\alpha 4\beta 7$.¹⁶ These integrin subunits bind specifically to ligands on the endothelium, known as addressins. The $\alpha 4\beta 1$ integrin binds to vascular cell adhesion molecule-1 (VCAM-1), whereas the $\alpha 4\beta 7$ integrin binds to mucosal addressin–cell adhesion molecule-1 (MAdCAM-1).¹ VCAM-1 and MAdCAM-1 are upregulated by inflammatory cells including TNF- α and interleukin-1 (IL-1), promoting the use of TNF inhibitors for IBD as well.

Two FDA-approved anti-integrin human monoclonal antibodies are currently approved for the treatment of IBD: natalizumab and vedolizumab. Natalizumab targets the $\alpha 4$ -subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins that are expressed on leukocytes.¹⁶ This interaction inhibits the $\alpha 4$ -mediated adhesion of leukocytes to VCAM-1 and MAdCAM-1, thus preventing migration of leukocytes into the cell and decreasing inflammation. Natalizumab is indicated in patients with moderately to severely active Crohn's disease with inadequate response to, or who are unable to tolerate, conventional therapies and TNF- α inhibitors.¹⁸ Vedolizumab has similar pharmacologic properties to natalizumab; however, it only inhibits the $\alpha 4$ -subunit adhesion of leukocytes to MAdCAM-1, not VCAM-1.¹⁹ Progressive multifocal leukoencephalopathy (PML) is a significant adverse effect of natalizumab due to inhibition of VCAM-1 activity.¹⁶ It has been hypothesized that preventing $\alpha 4\beta 1$ binding to VCAM-1 results in decreased immune surveillance within the

Table 1. Summary of Case Reports and Case Series Describing the Use of Biologic Agents in Patients with IBD After Liver Transplantation

Type of Study, No. of Patients	Median (Range) Age (yrs)	Indication for Liver Transplantation	Recurrent or De novo IBD	Immunosuppression After Liver Transplantation	IBD Treatment Before Liver Transplantation	IBD Treatment After Liver Transplantation	Clinical Outcome: Response rate (%)	Endoscopic Outcome: Mucosal healing (%)	Adverse Events
Case report ²⁰ (n=1)	29	PSC (n=1)	Recurrent (n=1)	Tac (n=1)	5-ASA (oral and enema), steroids, AZA (n=1)	IFX (n=1)	100	100	None
Case series ²¹ (n=2)	53.5 (43-64)	Fulminant hepatic failure (n=1) PSC (n=1)	Recurrent de novo (n=1)	Tac (n=1) Tac, MMF, pred (n=1)	Steroids and 5-ASA (n=1) 5-ASA and budesonide (n=1)	IFX (n=1) ADA (n=1)	100	NR	None
Case series ²² (n=8)	42 (22-69)	PSC (n=8)	Recurrent (n=8)	Tac, pred (n=2) Tac, pred, AZA (n=2) Tac (n=1) CsA, AZA (n=2) CsA, pred (n=1)	5-ASA (n=5) Immunomodulators: AZA, 6-MP and/or MTX (n=4) Steroids (n=6)	IFX (n=4) ADA → IFX (n=2) ADA (n=2)	87.5	42.9 (n=7)	Oral candidiasis, <i>Clostridium difficile</i> colitis, bacterial pneumonia, cryptosporidiosis, Epstein-Barr virus-positive post transplant lymphoproliferative disorder
Case series ²³ (n=6)	51.5 (28-65)	AIH (n=1) PSC (n=4) Biliary atresia (n=1)	Recurrent de novo (n=3)	Tac, MMF, pred (n=3) Tac, MMF (n=1) Tac (n=1) CsA, AZA (n=1) Tac (n=1)	NR	IFX (n=4) IFX → ADA (n=2)	67	NR	Systemic lupus erythematosus, colorectal cancer
Case report ²⁴ (n=1)	42	Subfulminant hepatitis (n=1)	de novo (n=1)	Tac (n=1)	NR	ADA (n=1)	100	NR	None
Case series ²⁵ (n=4)	39 (22-54)	PSC (n=4)	Recurrent (n=4)	Tac, pred, AZA (n=1) Tac, sirolimus (n=1) CsA (n=1) Tac (n=2) Tac, steroids (n=1) CsA (n=1)	NR	IFX (n=4)	75	33 (n=3)	<i>Molluscum contagiosum</i>
Case series ²⁶ (n=3)	43 (32-65)	PSC (n=3)	Recurrent (n=3)	Tac (n=1) Tac, steroids (n=1) CsA (n=1)	AZA (n=1) 5-ASA (n=1) NR	IFX (n=2) ADA (n=1)	NR	NR	None
Case report ²⁷ (n=1)	23	Biliary atresia (n=1)	De novo (n=1)	CsA (n=1)	Pred, AZA	IFX → VED (n=1)	100	NR	None
Case report ²⁸ (n=1)	40	PSC (n=1)	Recurrent (n=1)	NA	5-ASA, AZA (n=1)	IFX (n=1)	100	NR	None
Case report ²⁹ (2014) (n=1)	29	PSC (n=1)	Recurrent (n=1)	Tac, MMF, pred (n=1) Tac (n=17) CsA (n=1)	NR	IFX (n=7) ADA (n=7) IFX → ADA (n=4)	100	NR	None
Case series ³⁰ (n=18)	37.2 (24.0-51.9)	PSC (n=18)	De novo (n=18)	CsA (n=1)	NR	IFX (n=14)	38.9	64.3 (n=14)	Infection (undefined), colon cancer

(continued)

Table 1 (continued)

Type of Study, No. of Patients	Median (Range) Age (yrs)	Indication for Liver Transplantation	Recurrent or De novo IBD	Immunosuppression After Liver Transplantation	IBD Treatment Before Liver Transplantation	IBD Treatment After Liver Transplantation	Clinical Outcome: Response rate (%)	Endoscopic Outcome: Mucosal healing (%)	Adverse Events
Case series ³¹ (n=5)	42.4 (21–57)	PSC (n=4) AISC (n=1)	Recurrent (n=5)	Tac (n=2) Tac, MMF, pred (n=1) Tac, AZA, pred (n=1) Pred (n=1)	NR	VED (n=5)	NR	NR	Abnormalities in liver biochemistry
Case series ³² (n=5)	40.7 (32.5–68.7)	PSC (n=5)	Recurrent (n=3) de novo (n=2)	Tac (n=2) Tac, MMF, pred (n=1) Tac, MMF (n=1) Tac, pred (n=1)	5-ASA (n=1) AZA (n=1)	IFX → VED (n=5)	60	40	None
Case report ³³ (n=1)	20	PSC (n=1)	Recurrent (n=1)	NA	5-ASA, pred (n=1)	VED (n=1)	100	NR	NR
Case series ³⁴ (n=10)	36 (28.5–50)	PSC (n=9) Hepatitis C (n=1)	Recurrent (n=7) de novo (n=3)	Tac, MMF, pred (n=9) Basiliximab, Tac, MMF, pred (n=1)	5-ASA (n=9) AZA (n=4) IFX (n=3) ADA (n=3) VED (n=3)	VED (n=10)	60	NR	Cholangitis (n=4) <i>Clostridium difficile</i> colitis (n=4) Empyema (n=2) Pneumonia (n=1)

IBD = inflammatory bowel disease; PSC = primary sclerosing cholangitis; NR = not reported; AIH = autoimmune hepatitis; AISC = autoimmune sclerosing cholangitis; Tac = tacrolimus; 5-ASA = aminosalicylate; AZA = azathioprine; MMF = mycophenolate mofetil; pred = prednisone; IFX = infliximab; ADA = adalimumab; CsA = cyclosporine; 6-MP = 6-mercaptopurine; MTX = methotrexate; VED = vedolizumab.

central nervous system, in turn increasing the risk of PML.¹⁶ Other risks associated with anti-integrin monoclonal antibodies in the general population include infection, hepatotoxicity, and malignancy.¹⁷

Morbidity and mortality in liver transplant recipients are most commonly associated with posttransplantation complications, including infections. Therefore, the use of these biologic agents in an already immunosuppressed patient population raises the concern for an increased risk of adverse outcomes.

Literature Search

A literature search of the PubMed database (2002–2017) was performed to identify studies exploring the efficacy and safety of various biologic agents for recurrent or de novo IBD in liver transplant recipients. The following search terms were used: *biologics, liver transplantation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, and immunosuppression.*

Results

Demographic and Clinical Characteristics

Fifteen case reports and case series exploring the efficacy and safety of various biologic agents for recurrent or de novo IBD in liver transplant recipients were identified (Table 1).^{20–34} From these 15 case reports, we identified 67 patients who developed de novo or recurrent IBD after liver transplantation, and who also received anti-TNF or anti-integrin therapy. A majority of patients received liver transplants for PSC (60 patients [89.6%]), with other indications including fulminant hepatic failure, biliary atresia, subfulminant hepatitis, autoimmune hepatitis, and autoimmune sclerosing cholangitis. Of the 67 patients who developed IBD after liver transplantation, 38 patients (56.7%) developed recurrent IBD, whereas only 29 patients (43.3%) developed de novo IBD. Age at the time of transplantation ranged from 20 to 69 years.

Maintenance immunosuppression in these case reports and case series varied and included monotherapy or a combination of the following: tacrolimus, mycophenolate mofetil, prednisone, cyclosporine, basiliximab, and azathioprine. The majority of patients received tacrolimus (57 patients [85.1%]) either as monotherapy or as part of combination immunosuppression. Most patients received anti-TNF therapy for their IBD

after liver transplantation, with a majority receiving infliximab (39 patients [58.2%]) at some point, followed by adalimumab (20 patients [29.9%]). Only 22 patients (32.8%) of the liver transplant recipients were treated with vedolizumab for their IBD.

Clinical Course Following IBD Treatment

Of the 13 published case reports and case series reporting clinical response or remission of IBD activity in liver transplant recipients (59 patients), clinical response or remission of IBD was reported in 38 patients (64.4%). When comparing anti-TNF and anti-integrin therapies, the reported clinical response and remission rates in liver transplant recipients were 62.8% and 64.7%, respectively. The definition of clinical response or remission in these published articles was not consistent, with some reports using the Mayo Scoring System and others using the Physician Global Assessment or the Harvey Bradshaw Index. Mucosal healing, defined by absence of ulcerations on follow-up endoscopy, varied throughout the reported cases. Of the five published case reports and case series (30 patients) that reported on mucosal healing, 53.3% of patients had absence of ulcerations.

With respect to safety-related outcomes, based on the available literature, anti-TNF and anti-integrin therapy seems to be safe in liver transplant recipients. A majority of the cases did not report any significant adverse effects; however, a few cases highlighted infections and malignancy. A case series²² of eight patients with recurrent IBD after liver transplantation showed significant infectious complications including oral candidiasis, *Clostridium difficile* colitis, bacterial pneumonia, and cryptosporidiosis. The authors also reported a case of Epstein-Barr virus-positive posttransplantation lymphoproliferative disorder, which occurred 4 months after starting infliximab and 4 years after liver transplantation. Another case report²³ detailed a case of colorectal cancer in a patient with recurrent UC who received adalimumab after experiencing worsening IBD symptoms while receiving infliximab. Furthermore, a published abstract described the results of a meta-analysis of eight studies that evaluated 53 liver transplant recipients receiving anti-TNF therapy and 23 liver transplant recipients not receiving anti-TNF therapy (control group).³⁵ They reported that the overall infection rate for TNF-exposed patients was 0.12 compared with 0.15 in the control group, which

represented a nonsignificant relative risk ratio of 0.80 ($p=0.80$). It is important to consider that the mean follow-up time for these patients was not consistently reported, and many of the reports were published within 1 year from transplantation or diagnosis of IBD.

There were two case reports and three case series of patients with recurrent IBD after liver transplantation who were treated with vedolizumab. A case report²⁸ in 2015 demonstrated clinical response to vedolizumab with no significant adverse outcomes. A case series³¹ assessed the use of vedolizumab in 10 patients with PSC or autoimmune sclerosing cholangitis and IBD. Only five of the patients were liver transplant recipients. They reported clinical response using the Mayo endoscopy score in 40% of the patients; however, they did not delineate the results based on before or after liver transplantation, making it difficult to interpret the efficacy and safety of vedolizumab in liver transplant recipients. A more recent review of 10 OLT recipients³⁴ evaluated the use of vedolizumab for the treatment of moderate to severe IBD. The authors noted clinical improvement of IBD in 60% of the patients and reported that five patients experienced an infection following vedolizumab initiation, including *C. difficile* colitis, cholangitis, and empyema. No occurrences of opportunistic fungal, viral, or mycobacterial infections were reported. In these high-risk patients in all 15 case reports and case series, vedolizumab was used less frequently, which is one of the limitations that must be acknowledged. Since vedolizumab was FDA approved and brought to the market more recently (2014), these patients did not have an appropriate follow-up period to assess for the true safety and efficacy profile of this anti-integrin agent in liver transplant recipients. What is promising, however, is that vedolizumab is an available option in patients who are refractory to anti-TNF therapy and can possibly even be used before anti-TNF therapy with a theoretically lower chance to induce severe infections.

Conclusion

Patients undergoing liver transplantation secondary to PSC are at an increased risk for de novo or recurrent IBD, as well as other complications that may compromise graft outcomes. Therefore, the management of IBD in this high-risk patient population is a fine balance between safety and efficacy of IBD treatment, the transplanted

allograft, and infections. Data are limited to fully support or refute the use of biologic agents for IBD after liver transplantation; however, case reports and case series are available to help guide the use of these agents. Based on the limited available literature, the use of anti-TNF and anti-integrin therapy seems to be safe and effective after liver transplantation; however, the risks and benefits of these agents must be taken into consideration, and therapy must be individualized in a patient-specific manner. The safety outcomes of the biologics used in the patients in these reports were not as concerning as the risks labeled in their package inserts; however, a few occurrences of malignancy and mild infections were reported. Mechanistically speaking and from observations of anti-TNF and anti-integrin therapies in patients both with and without transplants, vedolizumab may be a safer option over anti-TNF therapy due to its gut specificity and potential decreased risk for infectious complications.

It is important to note that these case reports come with significant limitations. The only anti-TNF agents used in the patients in these reports were infliximab and adalimumab. Therefore, we are unable to extrapolate the findings to certolizumab or golimumab. Pertinent information was lacking in these reports, including maintenance immunosuppression dosing, goal tacrolimus and cyclosporine levels, therapeutic monitoring of biologic agents, production of anti-drug antibodies, and infection history before transplantation. More important, there are inconsistencies and a lack of information from the case reports and case series regarding the duration of treatment for IBD before transplantation and the time to recurrence of IBD. This information would allow for a better assessment of overall duration of immunosuppression and risk for adverse events. Future studies should consider including these data points to allow for better assessment.

Anti-TNF and anti-integrin therapies have demonstrated clinical remission rates of 36.4–39% in the general IBD population, with remission ranging from 4 to 56 weeks after initiation, excluding liver transplant recipients.^{13, 36, 37} Comparing remission rates in the general population with liver transplant recipients is difficult to assess given the heterogeneity in the patient population and the lack of randomized clinical trials in liver transplant recipients with IBD. More research is needed to confirm the true efficacy and safety of anti-TNF and anti-integrin therapy for IBD after liver transplantation.

Ideally, a prospective randomized study would help identify the safe and effective use of biologics after liver transplantation; however, given the limited number of patients undergoing liver transplantation for PSC who have IBD, large retrospective studies should be performed initially. In addition to the safe and efficacious use of biologics for IBD after liver transplantation, several questions remain unanswered including optimal maintenance immunosuppression regimens and screening for colorectal cancer and opportunistic infections in this high-risk patient population.

References

- Molodecky NA, Kareemi H, Parab R, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. *Hepatology* 2011;53:1590.
- Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012;56:1181–8.
- Bamias G, Nyce MR, De La Rue SA, Cominelli F. New concepts in the pathophysiology of inflammatory bowel disease. *Ann Intern Med* 2005;143:895–904.
- Verdonk RC, Dijkstra G, Haagsma EB, et al. Inflammatory bowel disease after liver transplantation: risk factors for recurrence and *de novo* disease. *Am J Transplant* 2006;6:1422–9.
- Henriksen EKK, Jorgensen KK, Kaveh F, et al. Gut and liver T-cells of common clonal origin in primary sclerosing cholangitis-inflammatory bowel disease. *J Hepatol* 2017;66:116–22.
- Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. *World J Gastroenterol* 2008;14(3):331–7.
- Lindkvist B, Benito de Valle M, Gullberg B, Bjornsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. *Hepatology* 2010;52:571–7.
- Rossi RE, Conte D, Massironi S. Primary sclerosing cholangitis associated with inflammatory bowel disease: an update. *Eur J Gastro Hepatol* 2016;28:123–31.
- Kochlar G, Singh T, Dust H, et al. Impact of *de novo* and preexisting inflammatory bowel disease on the outcome of orthotopic liver transplantation. *Inflamm Bowel Dis* 2016;22(7):1670–8.
- Roma MG, Toledo FD, Boaglio AC, et al. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. *Clin Sci* 2011;121:523–44.
- Indriolo A, Ravelli P. Clinical management of inflammatory bowel disease in the organ recipient. *World J Gastroenterol* 2014;20(13):3525–33.
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002;359:1541–9.
- Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;130(2):323–33.
- Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;357:228–38.
- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2014;146(1):96–109.e1.
- Ley K, Rivera-Nieves J, Sandborn WJ, Shattil S. Integrin-based therapeutics: biological basis, clinical use and new drugs. *Nat Rev* 2016;15:173–83.
- Ghosh S, Panaccione R. Anti-adhesion molecule therapy for inflammatory bowel disease. *Therap Adv Gastroenterol* 2010;3(4):239–58.
- Takeda Pharmaceuticals America, Inc. Entyvio [package insert]. Deerfield, IL; 2014.
- McLean LP, Shea-Donohue T, Cross RK. Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. *Immunotherapy* 2012;4(9):883–98.
- Lal S, Steinhart AH. Infliximab for ulcerative colitis following liver transplantation. *Eur J Gastro Hepatol* 2007;19:277–80.
- El-Nachef N, Terdiman J, Mahadevan U. Anti-tumor necrosis factor therapy for inflammatory bowel disease in the setting of immunosuppression for solid organ transplantation. *Am J Gastroenterol* 2010;105:1210–1.
- Mohabbat AB, Sandborn WJ, Loftus EV Jr, Wiesner RH, Bruining DH. Anti-tumor necrosis factor treatment of inflammatory bowel disease in liver transplant recipients. *Aliment Pharmacol Ther* 2012;36:569–74.
- Sandhu A, Alameel T, Dale CH, Levstik M, Chande N. The safety and efficacy of antitumor necrosis factor- α therapy for inflammatory bowel disease in patients post liver transplantation: a case series. *Aliment Pharmacol Ther* 2012;36:159–65.
- Bendezú García RA, Rodríguez Manrique MA, Hernández Martínez A, et al. Biological therapy for Crohn's disease in a liver transplant patient. *J Dig Dis* 2003;14:564–6.
- Indriolo A, Fagioli S, Pasulo L, et al. Letter: infliximab therapy in inflammatory bowel disease patients after liver transplantation. *Aliment Pharmacol Ther* 2013;37:835–43.
- Schnitzler F, Friedrich M, Stallhofer J, et al. Solid organ transplantation in patients with inflammatory bowel diseases (IBD): analysis of transplantation outcome and IBD activity in a large single center cohort. *PLoS One* 2015;10:1–19. <https://doi.org/10.1371/journal.pone.0135807>.
- Naito T, Shiga H, Endo K, et al. *De novo* Crohn's disease following orthotopic liver transplantation: a case report and literature review. *Intern Med* 2015;54:199–204.
- Meszaros M, Pageaux GP, Altwegg R. Management of ulcerative colitis using vedolizumab after liver transplantation for primary sclerosing cholangitis. *J Crohns Colitis* 2015;10:236.
- Karolina S, Chetan M. A unique case of biologic therapy for IBD post liver transplant. Abstract. In: *Inflammatory Bowel Disease*; 2014.
- Combes R, Altwegg R, Laharie D, et al. Efficacy and safety of anti-TNF therapy for inflammatory bowel disease (IBD) in liver transplant recipients for primary sclerosing cholangitis (PSC): a multicenter experience. Abstract. In: *European Crohn's and Colitis Organization*; 2017.
- Lim TY, Pavlidis P, Gulati S, et al. Vedolizumab in inflammatory bowel disease associated with autoimmune liver disease pre- and postliver transplantation: a case series. *Inflamm Bowel Dis* 2016;22(10):E39.
- Hartery K, O'Reilly S, Houlihan D, et al. Letter: vedolizumab for the management of inflammatory bowel disease in patients after liver transplantation for primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2017;45:373–9.
- Daffra PR, Etchevers MJ, Sobrero MJ et al. Use of vedolizumab in a transplanted liver patient: a case report of the first experience in a liver transplant referral center in Argentina. Abstract. In: *European Crohn's and Colitis Organization*; 2017.
- Wright AP, Fontana RJ, Stidham RW. Vedolizumab is safe and effective in moderate to severe inflammatory bowel disease following liver transplantation. *Liver Transpl* 2017;23:968–71. <https://doi.org/10.1002/lt.24757>
- Westerouen van Meeteren M, Anderson A, Hayee B, et al. Safety of anti-TNF treatment in liver transplant recipients – a meta-analysis. Abstract. In: *European Crohn's and Colitis Organization*; 2017.
- Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359(9317):1541–9.
- Faegan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.