Oral Budesonide for the Therapy of Post-liver Transplant De Novo Inflammatory Bowel Disease: A Case Series and Systematic Review of the Literature

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Background: The therapy for posttransplant IBD is clinically challenging. Patients receiving liver transplants are immunosuppressed to prevent rejection, but via an unknown mechanism develop de novo IBD in spite of receiving some of the same medications used for therapy in traditional IBD. In the published literature most of the patients who developed de novo IBD were treated with traditional corticosteroids. Exposure to systemic corticosteroids increases risks of infection, diabetes mellitus, and osteoporosis among other complications. Budesonide, a luminally active steroid with low systemic absorption, is an established therapeutic agent for IBD that should receive special considerations as first-line therapy in this patient population.

Methods: We describe 3 cases of de novo IBD after liver transplantation. None of these patients had a history of IBD prior to their transplant. All 3 were treated with oral budesonide in lieu of systemic corticosteroids. Additionally, a Medline MeSH search was performed using the terms "inflammatory bowel disease" and "liver transplant" as part of a systematic review of the literature.

Results: All 3 cases of de novo post transplant IBD went into clinical remission with oral budesonide. The Medline search ultimately revealed 19 case reports, case series or retrospective reviews on de novo post liver transplant IBD. Most reports focused on the diagnosis and risk factors and did not have an emphasis on therapy.

Conclusions: Given the track record for budesonide in traditional IBD, and its documented efficacy and systemic steroid-sparing benefit, in our opinion this drug should be considered first-line therapy for de novo posttransplant IBD.

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Key Words: liver transplantation, colitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis

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Diarrhea is a common problem among patients who have received a liver transplant. Increased risk of infection from immunosuppression, drug side effects, use of antibiotics, and comorbid diseases make the differential diagnosis of diarrhea broad. Various studies have shown an incidence of diarrhea in the post-solid organ and bone marrow transplant populations to be between 10%–43%.[1–3] The etiology of the diarrhea is unknown in as many as one-third of cases.[2] It is suspected that many of the cases of diarrhea may be due to undiagnosed inflammatory bowel disease (IBD). Most cases occur in patients with preexisting IBD, or in patients with risk factors for IBD like primary sclerosing cholangitis (PSC), but multiple studies have shown that de novo IBD is an increasingly recognized entity that occurs in this population in spite of ongoing immunosuppression.

There is a clear and historic association between IBD and several etiologies of chronic liver disease. Up to 70% of patients with PSC have ulcerative colitis (UC)[4] and ≈15% of patients with autoimmune hepatitis have IBD.[5] Many patients with chronic liver disease progress to endstage liver disease and liver transplant. These patients ultimately require lifelong immunosuppression. Studies of recurrent and de novo IBD after liver transplant are mixed, with reports of increased activity,[6–9] no change in activity/variable activity,[10] and decreased activity[11] of IBD. There is no clear consensus on proper therapy for these patients who develop IBD after liver transplant, but altering immunosuppression medications for these patients can be clinically challenging.

After liver transplant patients may be on multiple different immunosuppressants and still develop posttransplant IBD. Ironically, many of these medications are used in the therapy of IBD, such as azathioprine, tacrolimus, and corticosteroids. Prior case reports and case series have utilized 5-aminosalycylate (5-ASA) drugs and corticosteroids to treat recurrent and de novo IBD.[8,11–13] In some cases there was recrudescence of disease after steroid therapy was withdrawn. More recently, infliximab has been used as well.[14]

An underutilized approach to treating flares of IBD in this population is to use solely luminally active agents in an effort to avoid excessive systemic immunomodulation. Oral budesonide is a luminally active steroid with little systemic absorption due to its mucosal metabolism in the gut and

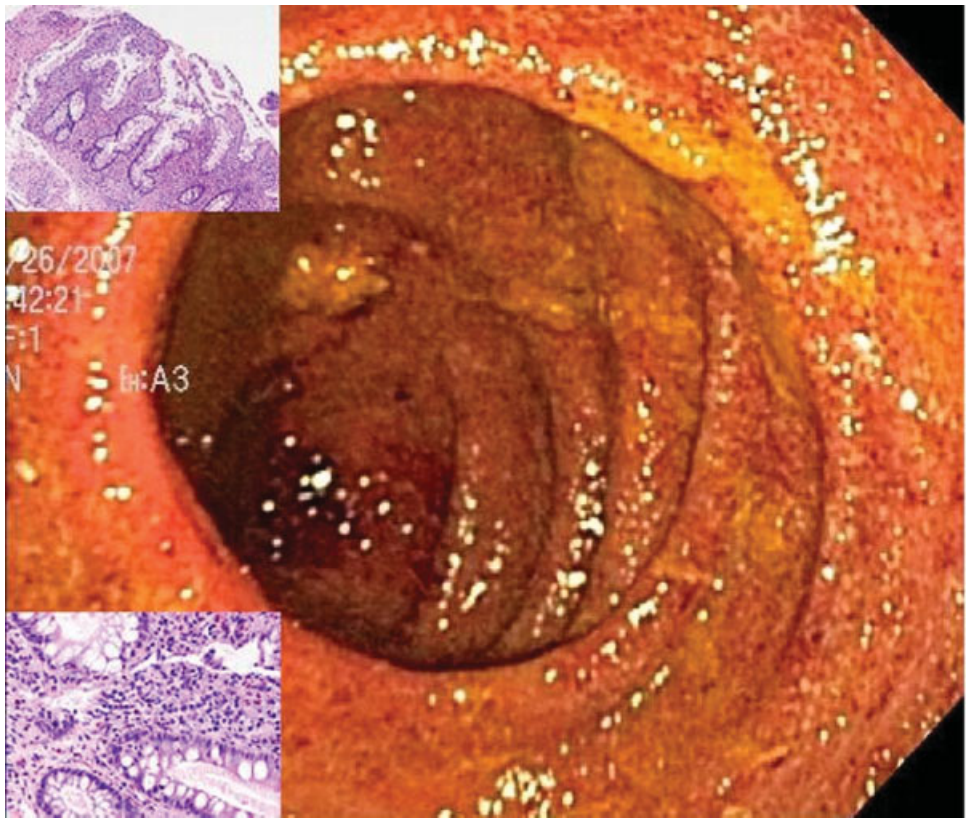

FIGURE 1. Case 1, right colon with low power (10x) inset (top) and high power (40x) inset (bottom). The low power biopsy demonstrates crypt architectural changes including crypt drop-out and irregularly shaped crypts with branching. These histologic changes infer "chronicity". The high power section of the colon biopsy reveals an area of cryptits, in which neutrophils are present within the colonic epithelium. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

"first-pass" metabolism in the liver.[15,16] Budesonide is currently used in patients with ileocolonic Crohn's disease (CD) and collagenous colitis and its effectiveness is also described in studies of patients with UD as well.[17,18]

Herein we present, to our knowledge, the first case series dedicated to patients after liver transplant with de novo IBD who were successfully treated with budesonide. Two prior case series have utilized this intervention, but the emphasis of those articles was on the natural history of post-transplant IBD and the diagnosis of de novo IBD, rather than therapy. To place this therapeutic approach into better perspective we also performed a systemic literature research of described therapies in patients with de novo IBD after liver transplantation.

MATERIALS AND METHODS

A Medline MeSH search was performed using the terms "inflammatory bowel disease" and "liver transplant." This search found 114 articles, 32 of which were reviews. Of these publications, 19 case reports, case series, or retrospective reviews were identified. The bibliographies of these articles were searched as well for additional studies relevant to de novo IBD after liver transplant.

Case Presentations

Case 1

A 46-year-old Caucasian female underwent a liver transplant for endstage liver disease due to autoimmune hepatitis-PSC overlap syndrome in February 2006. She had no antecedent problems with diarrhea or IBD. She had an unremarkable postoperative course and her immunosuppression regimen included tacrolimus, mycophenolate mofetil, and prednisone. Six months after transplant she developed a cytomegalovirus (CMV) infection that was successfully treated with ganciclovir.

Fourteen months posttransplant she started to have intermittently liquid stools with a frequency between 6–8 bowel movements daily. At that time her immunosuppression regimen consisted of mycophenolate, tacrolimus, and prednisone. Cessation of mycophenolate mofetil did not improve the diarrhea. A colonoscopy was performed that showed an inflamed ascending colon with less inflammation seen in the transverse colon, compatible with Crohn's colitis (Fig. 1). The terminal ileum, sigmoid colon, and rectum were unremarkable. Biopsy of inflamed areas of the colon showed mild chronic active colitis suspicious for IBD. The clinical symptoms did not improve with a therapy of mesalamine 4 g daily for ≈8 weeks. Next, therapy with budes-

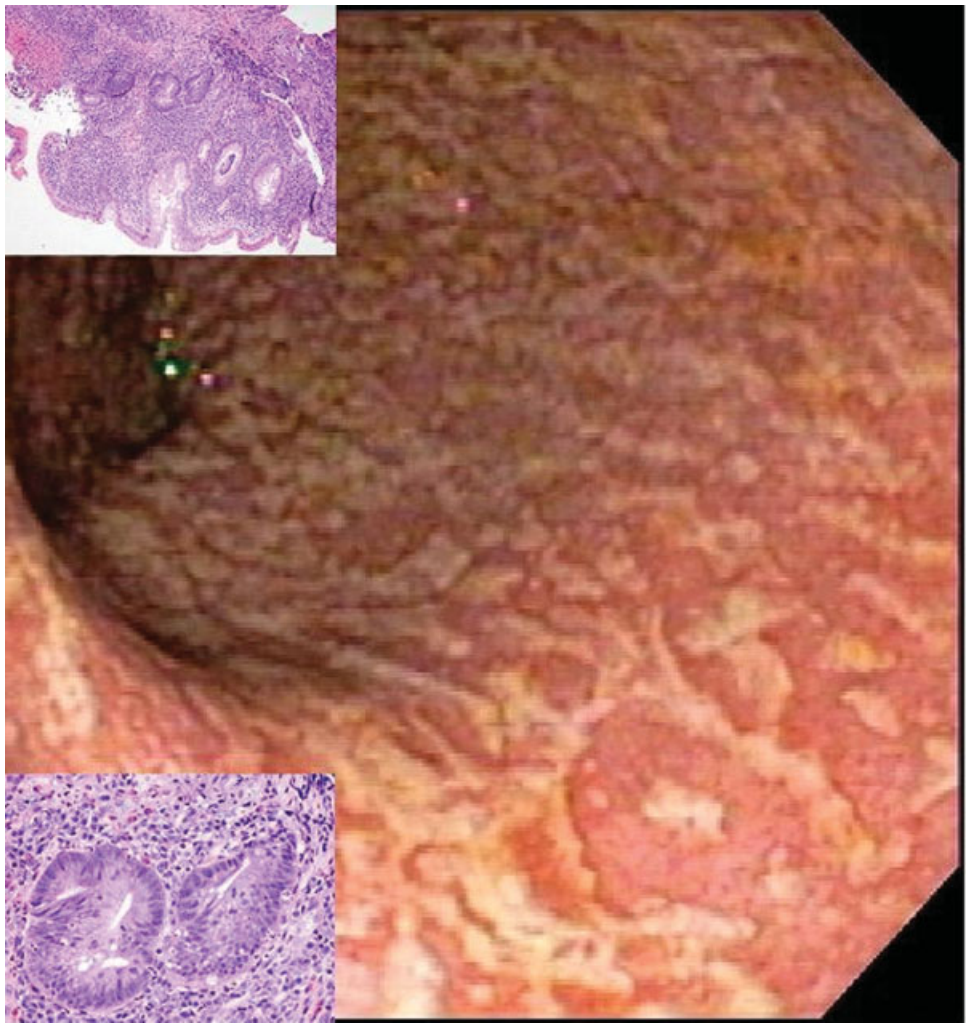

FIGURE 2. Case 2, left colon with low power (10x) inset (top) and high power (40x) inset (bottom). In the low power section, basal plasmacytosis (plasma cells involving the full thickness of the lamina propria), crypt drop-out and irregular crypt shape are present. High power view demonstrates cryptitis is present in this cross section of the colon biopsy. Notice the increased mixed inflammation in the adjacent lamina propria, including plasma cells and eosinophils. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

onide 9 mg/daily was initiated and the diarrhea completely resolved after 3 weeks. The budesonide was tapered by 3 mg every 4 weeks to 3 mg daily for 8 weeks and then completely stopped. As of March 2008 the patient remained in remission while on a maintenance dose of 4.8 g mesalamine daily.

Case 2

A 60-year-old Caucasian male, status post-liver transplant in 1994 secondary to PSC developed bloody diarrhea in November 2003 and was diagnosed with ulcerative pancolitis in 2004 at another institution. Colonoscopy at that time was consistent with UC; biopsies from the sigmoid colon showed moderate chronic active colitis and were negative for dysplasia. At the time of diagnosis his immunosuppressive regimen included cyclosporine 50 mg twice daily and mycophenolate mofetil 1 g twice daily.

Colonoscopy at our institution in March 2005 showed congested, erythematous, eroded, friable mucosa with contact bleeding in the entire colon, most consistent with severe ulcerative pancolitis (Fig. 2), which was confirmed by histology. The patient's IBD originally responded to high-dose prednisone, but he developed a steroid-dependent clinical course, with flares every time he tapered below 15 mg prednisone despite a concomitant mesalamine therapy (4.8 g daily).

In July 2007 budesonide 9 mg daily was started and the steroids were slowly tapered off. By September 2007 a full clinical remission was obtained. By December 2007 the budesonide was tapered to 3 mg every other day with a concomitant dose of 3.2 g mesalamine daily. As of March 2008 the patient remained in clinical remission.

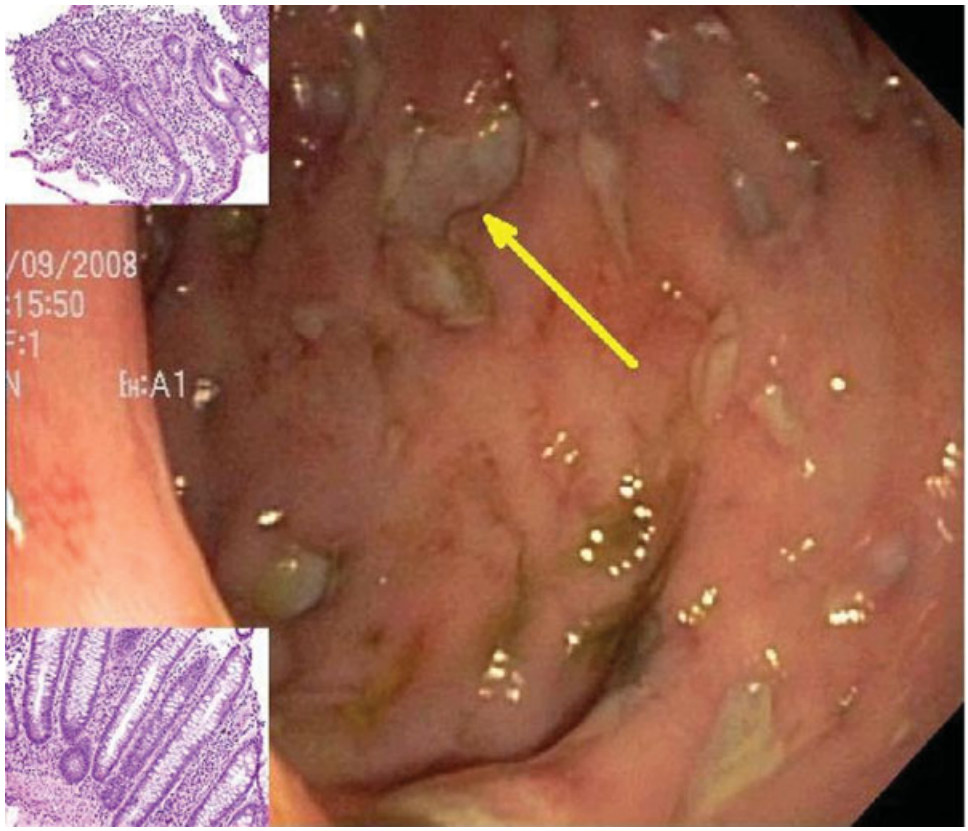

FIGURE 3. Case 3, right colon with two medium power (20x) biopsy insets. The top image shows a collection of neutrophils present within a crypt (crypt abscess). The bottom image demonstrates a focal area of cryptitis. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Case 3

A 52-year-old Caucasian female transplanted in 2000 for primary biliary cirrhosis presented to her local hospital in acute on chronic renal failure 7 years after transplant. She had a new onset of nausea, vomiting, and diarrhea with poor oral intake. Her immunosuppression at the time was 3 mg of sirolimus daily. One week prior to admission she received a 5-day course of amoxicillin for tooth pain. One month prior to admission she was tapered off tacrolimus and switched to sirolimus for calcineurin-induced renal insufficiency.

She responded rapidly to intravenous fluids and her renal function returned to baseline. Stool studies for enteric pathogens, *Clostridium difficile,* and ova and parasites did not reveal any infectious organisms. The patient was started on empiric metronidazole and her symptoms resolved.

Three weeks later the patient was transferred to our institution with return of her symptoms, a 25-lb weight loss, and pre-renal azotemia. Colonoscopy was performed and showed patchy erythematous and ulcerated mucosa in the sigmoid, descending, and transverse colon. Biopsies demonstrated colonic mucosa with cryptitis and focal crypt abscess formation. There were no viral cytopathic effect or granulomas identified. Despite a negative CMV polymerase chain reaction (PCR), CMV colitis was strongly suspected. The patient was started on ganciclovir for empiric CMV therapy and clinically improved.

In January 2008 the patient was admitted with the same symptoms and pre-renal azotemia. Repeat colonoscopy showed left-sided edema and worsening ulcerations in the right colon (Fig. 3). Biopsies were similar to prior results, viral cultures and serum PCR for CMV, herpes simplex virus, human herpes virus-6, and Epstein–Barr virus were negative. At this time a diagnosis of posttransplant IBD was entertained and the patient was started on 4 g mesalamine daily and 9 mg daily of budesonide. The patient had a rapid clinical recovery and went into clinical remission. Unfortunately, 4 weeks later she suddenly died from unrelated causes.

DISCUSSION

In our review of reported cases of de novo IBD after liver transplant we identified 19 case reports, series, and reviews that totaled some 62 patients with de novo posttransplant IBD (Table 1). The majority of these cases were characterized as UC, several as CD, and 2 as indeterminate colitis. One study did not specify the type of inflammation and there was 1 case of collagenous colitis. The majority of studies that reported treatment of de novo IBD utilized systemic steroids and 5-ASA agents.

TABLE 1. Studies reporting *de novo* IBD after liver transplant

Author	Year	Total # *de novo* IBD	#UC	#CD	Other	IBD Therapy
Shaked et al[28]	1992	3	3			Not specified
Cuoco et al[29]	1997	1	1			Not specified
Riley et al[30]	1997	12	8	4		5-asa, steroids
Befeler et al[11]	1998	1	1			5-asa, steroids
Chalasani et al[31]	1998	2	2			Not specified
Khan et al[13]	1999	3	3			5-asa, steroids
Safadi et al[32]	1999	2	2			Not specified
Ramji et al[33]	2002	2		2		5-asa, steroids
Wong et al[1]	2002	2	2			Steroids
Haagsma et al[19]	2003	6	3	1	2 (IC)	5-asa, budesonide
Papatheodoris et al[9]	2003	3	3			Steroids
van de Vrie et al[34]	2003	1	1			Steroids, CNI
Papadakis et al[35]	2004	1		1		Not specified
Ho et al[8]	2005	1	1			Steroids
MacLean et al[10]	2005	5				Not specified
Verdonk et al [36]	2006	8	7		1 (IC)	Not specified
Worns et al[20]	2006	5	5			5-asa, steroids, budesonide
Cholongitas et al[37]	2007	3	3			Steroids
Halsey et al[12]	2007	1			1(CC)	5-asa

Inflammatory bowel disease (IBD), Ulcerative colitis (UC), Crohn's disease (CD), 5-aminosalycylate (5-asa), Indeterminate colitis (IC), Collagenous colitis (CC), Calcineurin Inhibitor (CNI)

Two European case series, Haagsma et al,[19] from the Netherlands, and Worns et al,[20] from Germany, reported using budesonide in a minority of their patients, among other interventions.

Presented herein are 3 cases of de novo IBD after liver transplant. While this clinical entity has been reported in the medical literature in the past, there has been no consensus about appropriate therapy. Clearly, patients who have undergone liver transplant are immunosuppressed and the majority of medications used to prevent graft rejection also have some utility in treating IBD exacerbations or maintaining IBD remission. However, in patients who developed de novo IBD while already on systemic immunosuppression, a new therapeutic approach may be warranted. We submit the addition of a luminally active agent, oral budesonide, as first-line therapy or, as in Case 2, an approach to spare systemic steroids. Budesonide has known efficacy for therapy and maintenance of IBD and will not complicate an already complex medication regimen by significantly increasing systemic immunosuppression or by exposing patients to the untoward effects of systemic corticosteroids.

Budesonide is used for patients with IBD in either an oral, controlled released preparation or rectally as an enema-based preparation. Budesonide has a higher affinity for the steroid receptor than prednisone, dexamethasone, or hydrocortisone.[15] The systemic effects and unwanted side effects are limited by intestinal wall metabolism and first-pass metabolism in the liver, eliminating 90% of the drug, thus causing significantly less plasma cortisol suppression than the other glucocorticoids.[15,16]

Many of the original studies of budesonide focused on its efficacy in treating CD; these have been summarized in 2 large reviews. Kane et al[21] found that in CD patients with terminal ileitis and/or inflammation of the right colon, budesonide is more likely to induce remission when compared to placebo or 5-ASA product and has fewer systemic side effects than conventional corticosteroids. A recent Cochrane review by Otley and Steinhart[22] demonstrated similar findings.

Budesonide's utility is not limited to CD, however. Lofberg et al[17] have shown clinical remission rates for UC treated with an extended release formulation of budesonide approaching that of prednisolone, but without the suppression of morning cortisol levels. Budesonide has also been shown to be an effective systemic steroid-sparing agent in steroid-dependent UC.[18]

Budesonide has further value in the therapy of collagenous colitis. Bonderup et al[23] reported efficacy for budesonide in collagenous colitis in a randomized double-blind control trial. Lanyi et al[24] documented treatment successes of steroid refrac-

tory collagenous colitis with budesonide as well. These results, plus others, were compiled in a Cochrane review by Chande et al.[25] They not only documented clinical and histologic improvement when treating collagenous colitis with budesonide, but patients' overall quality of life was improved as well.

Ultimately, budesonide may be a viable therapeutic option for patients who develop de novo IBD after liver transplant, as there are data documenting efficacy for UC, CD, and collagenous colitis. Perhaps more important, however, is the lack of systemic side effects. Patients who are already immunosuppressed and have been exposed to the deleterious side effects of long-term corticosteroids would benefit from a steroid-sparing treatment alternative. In a study of patients with CD by Andus et al[26] where glucocorticoids were replaced by budesonide, there were significant reductions in moon facies, acne, obesity, hypertension, striae, "steroid skin," steroid myopathy, and edema. A similar study by Cortot et al[27] showed a 50% reduction in glucocorticoid-related side effects including improvement in acne, moon facies, and morning plasma cortisol levels.

Given the track record for budesonide in traditional IBD, and its documented efficacy and steroid-sparing benefit, in our opinion this drug should be considered first-line therapy for de novo posttransplant IBD. Further investigation is warranted, however, into the etiology of posttransplant IBD and investigation as to why this disease occurs in the setting of systemic immunosuppression.

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