

# World Journal of *Gastroenterology*

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## Inflammatory bowel disease in liver transplanted patients

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### Abstract

Most common hepatobiliary manifestation of

inflammatory bowel disease (IBD) are primary sclerosing cholangitis (PSC) and autoimmune hepatitis, ranking them as the main cause of liver transplantation (LT) in IBD setting. Course of pre-existing IBD after LT differs depending on many transplant related factors. Potential risk factors related to IBD deterioration after LT are tacrolimus-based immunosuppressive regimens, active IBD and cessation of 5-aminosalicylates at the time of LT. About 30% patients experience improvement of IBD after LT, while approximately the same percentage of patients worsens. Occurrence of *de novo* IBD may develop in 14%-30% of patients with PSC. Recommended IBD therapy after LT is equivalent to recommendations to overall IBD patients. Anti-tumor necrosis factor alpha appears to be efficient for refractory IBD. Due to potential side effects it needs to be applied with caution. In average 9% of patients require proctocolectomy due to medically refractory IBD or colorectal carcinoma. The most frequent complication in patients who undergo proctocolectomy with ileal-pouch anal anastomosis is pouchitis. It is still undeterminable if LT adds to risk of developing pouchitis in PSC patients. Annual colonoscopies are recommended as surveillance and precaution of colonic malignancies.

**Key words:** Inflammatory bowel disease; Anti-TNF alpha therapy; Liver transplantation; Immunomodulatory therapy; Immunosuppression; Proctocolectomy; Risk factors

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**Core tip:** Management of inflammatory bowel disease in setting of liver transplantation (LT) is a clinical challenge because of intermittent flares and remissions of the disease, regardless of post-LT immunosuppression to prevent organ rejection. In this article we report new insight on actual knowledge on diagnostic and treatment opportunities in pre- and post-transplant period.

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## INTRODUCTION

Liver transplantation (LT) is a routine treatment option for patients with end stage liver diseases including autoimmune diseases such primary sclerosing cholangitis (PSC), primary biliary cirrhosis and autoimmune hepatitis (AIH). The number of organ recipients with PSC and AIH is constantly increasing due to the increased number of newly diagnosed patients, inadequate treatment options and the increased availability of organ donors. Because of the overlap of various autoimmune diseases in high volume transplant centres, patients with inflammatory bowel disease (IBD) as well as PSC, AIH, or both are increasingly common. IBD is a chronic complex pathological immune response/inflammation of the gut, intestines, or both, and its prevalence is increasing in western world. Presumably, IBD is a consequence of the improper and continuous activation of the mucosal immune system sustained by physiological flora<sup>[1]</sup>. Three major subtypes usually categorise IBD: ulcerative colitis (UC), Crohn's disease (CD) and unclassified IBD. A close pathophysiological correlation exists between PSC and IBD prior to LT<sup>[2,3]</sup>. IBD is diagnosed in approximately 50%-80% of patients with PSC, with UC comprising approximately 80%-90% of these cases; however, CD (typically with colonic or ileocolonic involvement) can also occur<sup>[4]</sup>. Overall 2.4%-7.5% of patients with UC and 1.4%-3.4% patients with CD are at risk of PSC development<sup>[5,6]</sup>. Considering there is no effective medical treatment for PSC, liver transplantation (LT) is the only curative therapy for end-stage liver disease due to PSC at the moment<sup>[6]</sup>. Since PSC is highly prevalent in patients with IBD, it is the most common cause for LT in IBD patients.

Another form of chronic liver disease associated with IBD is AIH, an inflammation of unknown cause characterized by hypergammaglobulinemia, autoantibodies and specific liver biopsy finding<sup>[7]</sup>. The prevalence of IBD among patients with AIH is approximately 16% (mostly UC)<sup>[8]</sup>. In case of acute liver failure or decompensated liver cirrhosis, LT is the only treatment option for patients with AIH<sup>[9]</sup>.

Treating IBD in patients receiving LT is a clinical struggle because of intermittent flares and remissions, regardless of the significant postoperative immunosuppression needed to prevent organ rejection. *De novo* IBD after solid organ transplantation has been reported with an incidence estimated to be ten times higher than that of IBD in the general population<sup>[10]</sup>.

This review describes the evolution of pre-existing IBD and *de novo* IBD after LT, the clinical management of active IBD during the post-transplantation period with special consideration of colorectal carcinoma (CRC) surveillance.

## PRIMARY SCLEROSING CHOLANGITIS AND LIVER TRANSPLANTATION

PSC is an immune-mediated chronic and progressive cholestatic liver disease characterised by inflammation and fibrosis of both the intra- and extra-hepatic bile ducts. Both bile ducts are involved in the majority (up to 87%) of all patients' disease conditions; small-duct PSC is involved in 5%-20%, whereas large-duct PSC is less common<sup>[11]</sup>. Small-duct PSC appears to represent an early stage associated with a better prognosis than classic PSC, which rarely progresses to large-duct PSC.

Patients with concurrent PSC and IBD (PSC/IBD) represent a unique population of patients with IBD. They are typically younger with a higher occurrence of cholangiocellular carcinoma, LT or death than other patients with PSC<sup>[12,13]</sup>. IBD can be diagnosed at any time during the course of PSC; typically, however, it is diagnosed before PSC. The prevalence of PSC with concomitant CD (PSC/CD) is relatively rare, but the outcome is more benign than PSC with UC (PSC/UC) or without IBD. Unlike patients with other forms of CD, those with PSC/CD are less likely to smoke or have ileal disease involvement<sup>[14]</sup>. In comparison with the overall UC population, patients with PSC/UC tend to have milder bowel disease, a higher incidence of pancolitis (87% vs 54%), rectal sparing (52% vs 6%) and backwash ileitis (51% vs 7%)<sup>[15,16]</sup>. PSC/CD patients characteristically have colonic or ileocolonic involvement, small duct PSC (25% patients), and are more likely to be female. Compared with patients with PSC/UC, those with PSC/CD have less IBD flares associated with lower rate of progression to cancer, LT or death, suggesting a biologically different progression risk in two diseases<sup>[17]</sup>.

An negative relationship exists between the severity of PSC and the severity of IBD. Progressive PSC requiring LT, reflected by a higher Mayo PSC risk score, is associated with a decreased need for colectomy. The possibility of lymphocyte trafficking in this phenomenon has not been fully explored<sup>[16,18,19]</sup>. Because of the inverse relationship between the activity of PSC and UC, patients who require LT might be expected to have a worsening of underlying UC after LT. Despite the strong association, the two diseases progress independently of each other.

The risk of CRC is ten-fold higher in patients with PSC/UC than the general population<sup>[20]</sup>. The development of neoplasia (dysplasia or colorectal carcinoma) is four times higher in the PSC/UC population than the overall UC population. The cumulative 10-year risk is between 0% and 11%<sup>[21,22]</sup>. However, a less significant



**Table 1** Efficacy of immunosuppressive and inflammatory bowel disease treatment after liver transplant

Drug	Anti-rejection therapy	IBD therapy	IBD efficacy	Potential risks	Ref.
Prednisone	Yes	Induction	Reduction of flare up	Infectious, metabolic side effects risk of PSC recurrence	[40,48]
5-ASA	No	Induction/ Maintenance	80% reduction of flare up 53% induction of remission in recurrent IBD 75% induction of remission in de novo IBD	Possible leukopenia with AzA	[15,16,41,48]
AzA	Yes	Induction/ Maintenance	IBD-free survival at 5-years 88%	Leukopenia, pancreatitis, infections, malignancy	[43]
anti-TNF-alpha	No	Induction/ Maintenance	clinical improvement 78% (range 50%-100%) mucosal healing 33%-43%	Infective, autoimmune, neoplastic side effects	[47,91-97]
Tac	Yes	No	Up to 64% flare up (4-fold increased risk) risk of infectious side effects	Infective, metabolic, neoplastic side effects	[35,36,38,43,41]
CsA	Yes	UC induction	In combination with AZA up to 30% flare up risk of side effects	Infective, metabolic, neoplastic side effects	[41]
MMF	Yes	No	ND	Pancitopenia, GI side effects	[51]

LT: Liver transplant; IBD: Inflammatory bowel disease; TNF: Tumor necrosis factor; UC: Ulcerative colitis; CD: Crohn's disease; Tac: Tacrolimus; CsA: Cyclosporine; AZA: Azathioprine; MMF: Mycophenolate mofetil; ND: Not determined; GI: Gastrointestinal.

association exists among patients with CD. In the study of Navaneethan *et al.*<sup>[16]</sup> more patients with PSC/UC developed colon neoplasia than PSC/CD (35.9% vs 18%). Patients with UC had a 56% higher risk of developing colon neoplasia than CD. The colectomy-free survival and LT-free survival rates did not significantly differ between the IBD groups. Moderate-to-severe disease activity on endoscopy at the time of diagnosis and the duration of UC or CD independently increased the risk of developing any colon neoplasia<sup>[16]</sup>.

In patients with PSC without known UC screening colonoscopy, multiple rectal biopsies should be performed at the time of diagnosis and, if negative, repeated every 5 years thereafter because many of these patients are asymptomatic. Patients with PSC with known UC should have colonoscopies during their initial evaluations and every 1-2 years thereafter because of the increased risk of neoplasia<sup>[23]</sup>. Pancolonoscopy with methylene blue or indigo carmine chromoendoscopies should be performed during surveillance colonoscopy, with targeted biopsies of any visible lesion<sup>[24]</sup>. Meta-analysis examined the diagnostic accuracy of chromoendoscopy compared with histology and reported a sensitivity of 83.3% and a specificity of 91.3% for chromoendoscopy regarding the detection of intraepithelial neoplasia<sup>[25]</sup>. Chromoendoscopy also aids in the discrimination between neoplastic and non-neoplastic changes based on surface crypt architecture (pit pattern). If appropriate expertise for chromoendoscopy is unavailable, then random biopsies (ideally 4 every 10 cm) should be performed. In addition, any suspicious lesions, mucosal irregularity or masses should be biopsied<sup>[26]</sup>. However, this option is inferior to chromoendoscopy regarding the detection rate of neoplastic lesions<sup>[27,28]</sup>.

Multiple medical therapies have been studied in PSC with limited success. LT remains the only option for

patients with PSC who develop complications of end-stage liver disease or disease-specific complications such as recurrent episodes of bacterial cholangitis, intractable pruritus, and cholangiocellular carcinoma (in carefully selected patients)<sup>[6]</sup>. The evaluation of patients with PSC for LT is inherently difficult because of the unpredictability of the disease course and the high risk of biliary tract malignancy. Disease-specific complications can arise at any time during the disease course. Several prognostic models have been developed to assist clinicians to predict the natural history of PSC; one of the best known is the Mayo Risk Score. Current guidelines do not recommend any specific model to predict clinical outcomes in individual patients because no consensus exists concerning the optimal method to apply<sup>[5]</sup>. Consequently, the general criteria for LT do not differ between PSC and other chronic liver diseases; the Model of End-stage Liver Disease applies the liver allocation procedure identically to other indications.

Currently, no specific guidelines exist for the medical management of patients with PSC and active IBD before LT. Additional prospective controlled studies are needed to deliver specific recommendations regarding the PSC/IBD population. Until then, patients should be treated similarly to other patients with IBD according to general guidelines, knowing the risk of immunomodulatory therapy side effects, and these effects should be controlled before the patient assumes a position at the top of the transplant list. The introduction of any immunomodulatory therapy in patients with PSC/IBD should be weighed against risk of liver or infectious disease deterioration (Table 1). Alternatively, attempts to minimise immunomodulatory therapy in stable patients at the top of the list to reduce the chance of an opportunistic infection should be individually and carefully weighed against the



potential of disease flare<sup>[29,30]</sup>.

If colonic neoplasia is present, then total colectomy should be reconsidered before LT. Each case must be carefully assessed for the potential risks and benefits and considered individually because no data from controlled studies exist regarding this problem, and general recommendations on an optimal approach are lacking. Colonic resection in face of end-stage-liver-disease might be associated with increased morbidity and mortality. Alternatively, the approach of delaying a resection until a suitable time after LT increases the chance that the malignancy is already present and risks further aggravation with immunosuppression or uncontrolled active disease refractory to medical therapy.

## RISK FACTORS ASSOCIATED WITH EXACERBATION OR *DE NOVO* IBD AFTER LIVER TRANSPLANTATION

The course of IBD after LT is highly variable. The development of *de novo* or the worsening of pre-existing IBD after an LT might have different pathogenic pathways than traditional IBD. This course might be affected by the possible cessation of the pre-transplant protective effect of PSC activity and different immunosuppressive regimens after LT. The interpretation of the results from previously published studies is complicated because of the small number of included patients, the differences in inclusion and exclusion criteria, diagnostic and treatment procedures, statistical analyses and duration of follow up. Some questionnaire-based studies have reported significant improvements in IBD activity (59%-82% of patients reported improved symptoms), whereas other studies have shown a deterioration of IBD course (in up to 50% of patients), with 30% of patients experiencing repetitive flares<sup>[31-34]</sup>. Dvorchik *et al*<sup>[35]</sup> suggested that LT and the concomitant use of immunosuppression triple the rate of IBD progression and the need for colectomy. The Nordic Transplant registry of 439 PSC liver recipients revealed increases in post-transplant overall IBD activity, colonic inflammation and the number of relapses. Although not significant, a trend of a higher risk for colectomy due to increased disease activity was observed<sup>[36]</sup>. In 2013, Singh *et al*<sup>[37]</sup> analysed the evolution of IBD after LT for patients with PSC. This analysis included 14 studies of 609 patients receiving LT with inactive IBD at the time of LT and a follow-up period of approximately 4.8 years (range, 1.8-7.2 years). Three different patterns of the disease courses were almost equally distributed across the patients: 31% improved, 39% were stable and 30% worsened. After 5 and 10 years, the cumulative risks of disease exacerbation were 39%-63% and 39%-98%, respectively<sup>[37,38]</sup>.

At the moment, it is not possible to correlate age, gender, duration or severity of PSC disease, the extent

and type of IBD (UC or CD), or pre-transplant IBD treatment (immunomodulator or corticosteroids) with the upcoming post-transplant clinical IBD course<sup>[34,35,37,38,39,40]</sup>. Verdonk *et al*<sup>[41]</sup> reported that clinically active IBD at the time of LT is related to a threefold higher risk for a post-transplant IBD flare up. In addition, Befeler *et al*<sup>[42]</sup> reported more favourable IBD outcomes with inactive disease at the time of LT, emphasising the importance of proper IBD treatment before LT. According to Joshi *et al*<sup>[38]</sup> smoking is an additional risk factor for pre-existing IBD worsening at the time of LT. Nevertheless, the pre-transplant use of immunomodulators, corticosteroids, or both along with a lower level of IBD activity does not universally predict favourable post-transplant IBD courses<sup>[37,38,40]</sup>.

The risk of *de novo* IBD after LT for patients with PSC is significantly lower than the rate of recurrence (10%-11% after 5 years, and 14%-30% after 10 years, respectively)<sup>[41,43]</sup>. However, the incidence of *de novo* IBD after solid organ transplantation is 10 times higher than that among the overall population (20/100000 patients year vs 206/100000 patients year), and at most related to patients with PSC receiving LT<sup>[10]</sup>. The published median time to IBD exacerbation is 1 year (range, 0.3-8.6 years), and it is approximately 4 times longer (3.9 years, range 1.1-7.1 years) for *de novo* IBD<sup>[38,41,43]</sup>. Verdonk *et al*<sup>[41]</sup> studied 91 LT recipients with PSC and found that 19% developed *de novo* post-transplant IBD disease, the majority of them (63%) with AIH, and all but one with an indeterminate result developed UC. *De novo* IBD after LT is also observed in patients who receive LT for non-PSC indications such as autoimmune hepatitis, Wilson's disease and hepatitis B. The pathophysiology of this seemingly paradoxical phenomenon is poorly understood<sup>[37]</sup>.

The possible different patterns of disease course in two IBD entities (UC and CD) is difficult to obtain because of the small number of patients with CD in most studies; the authors rarely report separate results for two IBD entities; and the influence of other factors on disease course. In one study, the rate of disease exacerbation was higher in patients with UC (73%) than those with CD (38%)<sup>[41]</sup>.

The role of citomegalovirus (CMV) infection in IBD after LT is controversial. Tissue-invasive GI tract CMV disease during the post-transplant period commonly manifests with symptoms that are indistinguishable from IBD. In addition, CMV is a potent up-regulator of alloantigens and thereby increases the risk of allograft rejection. In transplanted patients with IBD, the immunomodulatory effects of CMV might be related to the modulation of local and systemic immune responses to other GI pathogens, increased intestinal permeability, the expression of vascular cell adhesion molecule 1, the up-regulation of major histocompatibility complex 1, and increased mucosal interleukin-6 production<sup>[41]</sup>. Previous studies have suggested that only CMV mismatch positively influences

*de novo* post-transplant occurrence (RR = 4.5) because other studies have been unable to confirm these data regarding the recurrence of pre-transplant established IBD<sup>[38,39,41,42,44]</sup>. To detect recipients at high risk of post-transplant CMV disease, all recipients and donors should be screened for serum antibodies to CMV. CMV prophylaxis based on valganciclovir for at least 3 mo should be implemented for all patients at a high risk of developing CMV infection, including the use of CMV-seropositive donors in CMV-seronegative recipients, the treatment of acute rejection episodes, and the use of intense immunosuppression. The detection of viremia *via* CMV-PCR, in all suspected patients, is essential for the early diagnosis of CMV infection. Treatment with ganciclovir or valganciclovir should be implemented for patients with persistent or increasing viremia (CMV infection) and in all individuals for whom CMV infection evolves into CMV disease<sup>[45]</sup>.

The empirical reinitiating of 5-ASA directly after LT likely protects against the worsening disease activity of IBD after LT, with an estimated 80% decrease in risk of flare-ups, proctocolectomy, or both<sup>[15,16]</sup>. In almost all published studies, patients with UC represent majority (80%-90%), with only small number of CD patients (typically with colonic or ileocolonic involvement). Most authors did not provide details on type of IBD (CD or UC) while concluding that 5-ASA have positive effects in post-transplant IBD treatment. From experience in overall IBD population, 5-ASA is effective treatment option in patients with colonic IBD involvement.

Considering CNI-based regimens after LT and their correlation with IBD during a 1- to 5-year period, 13%-64% of patients receiving tacrolimus and 4-10% receiving tacrolimus-free regimens have experienced IBD flare-ups<sup>[35]</sup>. Similarly, retrospective studies have confirmed that tacrolimus increases the risk of post-transplant IBD relapse by four times<sup>[41,43]</sup>. Haagsma *et al*<sup>[43]</sup> previously described a cumulative risk of 11% for patients with IBD after 5 years in a prednisone/cyclosporine/azathioprine treatment group vs 42% in a prednisone/tacrolimus treatment group. This finding is similar to the risk of 41% observed after 5 years for patients using prednisone/tacrolimus found by Verdonk *et al*<sup>[41]</sup>. A study evaluating the Nordic Liver Transplant Registry data regarding the post-transplant course of 439 patients with PSC revealed that an age younger than 20 years at diagnosis of IBD and the use of dual therapy with tacrolimus and mycophenolate mofetil (MMF) were significant risk factors for the worsening of IBD (HRs = 1.8 and 3.9, respectively), whereas a dual treatment with CsA and AZA revealed a significant protective effect (HR = 0.4). *De novo* IBD-free survival was decreased significantly among patients receiving tacrolimus vs those who did not<sup>[36]</sup>. Tacrolimus can suppress interleukin-2, thereby generating T-regulatory lymphocytes; it enhances the risk of pathological change in bacterial gut microflora as well as increases gut infections, intestinal

permeability, exposure of the intestinal mucosa elements to the immune system and, therefore, IBD evolution<sup>[37,41,43,46]</sup>. However, it is inconclusive whether all tacrolimus-based regimens are universally associated with an increased risk of IBD flare-up and the need for proctocolectomy after LT<sup>[33,39,41,47,48]</sup>. In addition, not all cyclosporine-based regimens have a worsening effect on the course of IBD<sup>[39,41]</sup>. Cyclosporine favourable effects have also been confirmed with regard to the treatment of severe, steroid-resistant UC in the overall population<sup>[49]</sup>. Although cyclosporine, and possibly tacrolimus, effectively induce remission in patients with steroid-resistant UC, these drugs are not effective for maintaining long-term remission in the overall IBD population.

Systemic corticosteroid therapy is applied to post-transplant IBD patients to prevent acute and chronic allograft rejection and induce IBD remission; however, this therapy remains inadequate to maintain remission and for endoscopic healing in patients with IBD. Prednisone therapy might positively affect the course of post-transplant IBD and the need for colectomy, but it is also linked to important side effects that require its controlled application<sup>[40,48]</sup>. Prolonged steroid therapies are an indirect risk factor for PSC recurrence by altering the immune response<sup>[50]</sup>.

Although the exact role of MMF in IBD is not defined, its application is related to gastrointestinal side effects that mimic IBD flare-ups<sup>[51]</sup>.

Azathioprine and 6-mercaptopurine were among the first anti-rejection agents used in solid organ transplantation and showed reasonable efficacy. They have since fallen out of favour partially because of a perceived higher side effect profile given that the doses required to prevent rejection often led to cytopenias and hepatotoxicity. However, the evidence for a significant benefit in terms of preventing acute cellular rejection using MMF rather than AZA is poor. Only two randomised controlled trials directly compared MMF with AZA with one update, and no difference was found between these treatments in terms of patient or graft survival<sup>[52-54]</sup>. In patients with IBD, however, MMF with AZA remain among the most used drugs for maintaining remission with proven efficacy in both patients with CD and those with UC. Azathioprine serves as a protective as immunosuppressant after LT among people with IBD. Based on 1- and 5-year follow-up assessments, the IBD-free survival rates of patients treated with azathioprine were 96% and 88%, respectively, compared with 87% and 54%, respectively, of untreated patients<sup>[36,43]</sup>. Unlike cyclosporine and tacrolimus, azathioprine is an effective and accepted therapy for preventing relapses among patients with CD or UC and the overall IBD population<sup>[49]</sup>.

The data concerning mTOR treatment for IBD are limited and whether mTOR can control disease activity in patients with IBD is currently not established<sup>[55]</sup>.

## DIAGNOSTIC ALGORITHM

Diarrhoea is the most common sign related to a post-transplant IBD flare-up. Because approximately 43% of patients suffer from various causes of diarrhoea after LT, this condition requires exact an identification of the underlying aetiology, whether it is the consequence of an infection, drug application, dietary modification, small intestinal bacterial overgrowth, IBD, or other cause<sup>[56]</sup>. MMF is more commonly associated with diarrhoea than other immunosuppressive agents (11.6% of patients)<sup>[57]</sup>. Antibiotics and dietary modifications during the post-transplant period can also cause diarrhoea. A stool sample analysis must be performed to identify infection agents such as enteropathogenic bacteria, especially *Clostridium difficile* toxin, which is a common cause of IBD exacerbations during the pre- and post-transplant periods<sup>[58]</sup>. CMV disease can be confirmed with positive blood samples of PCR, pathognomonic changes on bioptic samples of infected tissue (bulls eyes), or both. Colonoscopy is mandatory to confirm *de novo* or recurrent IBD, evaluate the severity and extension of the disease, exclude other aetiologies or neoplasia and evaluate therapy success. Regular follow-up examinations with biopsies should be performed in suspected cases of disease exacerbation, to screen for neoplasia, or both.

## TREATMENT OF POST-TRANSPLANTATION INFLAMMATORY BOWEL DISEASE

The high number of patients with IBD deterioration after LT illustrates the importance of close follow-up evaluations to optimise IBD treatment. Considering the known association between colonic inflammation and the development of neoplasia as well as the high risk of colorectal cancer (CRC) after LT, efforts should be made to restrict IBD activity after transplant. Knowing the influence of IBD remission at the time of LT on the post-transplant course it is of great importance to achieve remission even before the LT and to evaluate indications for proctocolectomy among selected patients with medically refractory IBD or at high risk of CRC.

Most of the data used to treat IBD in the post-transplant setting come from retrospective, uncontrolled studies on a small number of patients. Comparisons of these studies are hampered by the differences in study design, the number of patients, the length of follow-up and the level of details presented with regard to the studied patient population. Regarding these overall scarce data, no general recommendations exist for guidelines on specific treatments of patients with PSC/IBD during the post-transplant period. The proposed approach is mostly based on data from published uncontrolled retrospective studies and the application

of general scientific recommendations to treat patients with IBD (Table 1).

In most studies at the time of LT, patients were without therapy or on 5-ASA; only a few patients were on immunomodulatory therapy, especially anti-TNF-alpha<sup>[41,43]</sup>. Verdonk *et al.*<sup>[41]</sup> examined 91 patients receiving LT with PSC or AIH (75% PSC, 13% AIH), and 54% had IBD before LT. All patients had colonic involvement (90% UC, 8% CD, and 2% indeterminate disease). Approximately two-thirds (69%) of patients with IBD were on medication (59% 5-ASA, 6% prednisone, 4% AZA) at the time of LT. Because of the small number (4%) of patients with active disease at LT, IBD therapy was frequently discontinued preoperatively. Only some patients (mainly those with positive symptoms before LT) received empirically restarted 5-ASA. The majority (65%) of patients with PSC/AIH-IBD and pre-existing IBD developed exacerbation. After established IBD recurrence or *de novo* disease, patients were treated with 5-ASA, prednisone, AZA, or some combination therein. Complete remission occurred in 53% of patients; partial remission occurred in 19% of patients with recurrent IBD; and 8% patients underwent proctocolectomy because of intractable disease. A high number of patients with *de novo* IBD achieved complete remission (75%), and none needed surgery. The empirical reinitiating of 5-ASA directly after LT likely protects against the worsening disease activity of IBD after LT, with an estimated 80% decrease in risk of flare-ups, proctocolectomy, or both<sup>[15,16,48]</sup>.

Comparing the effects of the immunosuppressive agents used in LT anti-rejection or IBD management, great differences exist in efficacy, dosage, indications and the mode of actions between these treatment strategies. These differences might be influenced by differences in involved tissues and the pathogenesis of the different, although related, diseases<sup>[59]</sup>. In most of published data on treatment of IBD in PSC patients' analysis was of retrospective nature, immunosuppressive drugs were not prescribed regarding risk of IBD recurrence and most of the patients were treated with calcineurin inhibitors (mainly tacrolimus). Calcineurin inhibitors (*i.e.*, cyclosporine and tacrolimus) are highly effective as chronic therapies in solid organ transplantation and remain the first line agents at many institutions. In contrast, cyclosporine has limited utility among patients with IBD; it is used primarily in cases of fulminant UC and shows no proven efficacy with regard to CD. Tacrolimus is also largely ineffective for patients with IBD, with only a marginal improvement in fistulising CD<sup>[29]</sup>. Although convincing data is lacking, knowing the possible negative effects of tacrolimus and MMF on the course of post-transplant IBD (in case of active IBD with a low risk of graft rejection) is important. Preferential immunosuppressive regimens might be based on cyclosporine (over tacrolimus), azathioprine (over MMF), or both. When deciding on the optimal

immunosuppressive approach for individual PSC/IBD patients, it is important to evaluate for the potentially increased risk of acute and chronic graft rejection for non-tacrolimus based regimens, especially because this risk is likely relatively high in patients receiving LT with PSC or AIH<sup>[60]</sup>. To fully compare the two CNI, additional studies are needed. A prospective study comparing the triple regimen of cyclosporine/azathioprine/prednisolone with others such as azathioprine/tacrolimus or rapamycin-containing regimens would be useful.

For patients with active IBD, recommended IBD therapies within the post-transplant setting are equivalent to recommendations for the overall IBD population<sup>[29,47]</sup>. Several facts must be considered when choosing the optimal treatment approach: drug potency and safety profile (especially interactions with other immunosuppressant's), previous response to therapy in cases of IBD relapse, co morbidities (especially infections and neoplasia), type, severity, extension and extraintestinal manifestations of the disease. Although robust data to supporting the use of immunomodulators or biologics are not available, the limited data from case series show that these medications can be used safely.

Depending on the severity and extension of the disease, first line treatment of patients with mild-moderate UC should begin with oral 5-aminosalicylates (5-ASA) > 2 g/d, combined with topical mesalazine if tolerated, to boost remission rates<sup>[47]</sup>. 5-ASA therapy decreases the risks of flare-ups and proctocolectomy for approximately 80% of patients<sup>[41,48]</sup>. In some cases, 5-ASA interacts with azathioprine and increases the risk of leukopenia<sup>[37,61]</sup>.

Budesonide (9 mg/kg) has been shown to induce the remission of terminal ileitis and inflammation of the colon with fewer systemic side effects than conventional corticosteroids among non-transplant patients with IBD; moreover, budesonide is an effective steroid-sparing agent. In liver transplant patients already receiving systemic immunosuppression, budesonide can be considered as a first-line therapy for *de novo* post-transplant IBD to spare the use of systemic steroids. Although it has not been investigated in large randomised controlled trials, this approach has been effective in case series of *de novo* IBD in the post-transplant setting<sup>[62]</sup>. Moderate-to-severe IBD flare-ups should be treated with corticosteroids (e.g., a prolonged taper with oral or intravenous induction)<sup>[29,30,49]</sup>. In severe cases, corticosteroids are generally applied intravenously using methylprednisolone (60 mg/24 h), and the response is optimally assessed on the third day of application. Higher doses than those recommended are not more effective, whereas lower doses are less effective<sup>[49]</sup>. Immunosuppression with azathioprine (2.0-2.5g/kg per day) is shown to be effective as maintenance therapy after corticosteroid application<sup>[63]</sup>.

Because most patients receiving LT are already on immunosuppressive protocols with calcineurin inhibitors (e.g., cyclosporine and tacrolimus), second line therapies include biological therapy (e.g., infliximab and adalimumab)<sup>[49]</sup>. The overall published number of patients receiving LT with severe IBD started on anti-TNF-alpha treatment is currently limited (31 patients). Consequently, data concerning the long-term efficacy and side effects of this treatment are limited regarding their implementation. Of the 31 patients receiving LT who were submitted to anti-TNF-alpha therapy, 24 showed a clinical response (77.42%); the mucosal healing rate approached 43%, and the ability to taper off corticosteroids occurred in 83.3% of patients. However, 7 patients had serious infections (22.58%), and 2 patients developed malignancies (6.45%). No mortalities were reported. The potential side effects of biological therapy in the post-transplant setting might be severe (mostly related to malignancy, infection and autoimmune diseases); thus, cautious administration and vigilant patient re-evaluation are required<sup>[37]</sup>.

Compared with patients with recurrent IBD, those with *de novo* IBD responded better to medical therapy and needed fewer proctocolectomies<sup>[41]</sup>.

In cases of IBD refractory to conventional medical treatment, surgery should be considered as an alternative therapeutic approach.

## PROCTOCOLECTOMY

In cases of acute severe colitis, medically refractory colitis, dysplasia or colorectal carcinoma, surgery remains a subsequent treatment option<sup>[49]</sup>.

The overall need of proctocolectomy after LT is approximately 35%<sup>[37]</sup>. Several studies have reported that proctocolectomy was required after LT due to medically refractory disease or severe IBD flare-ups in 9% of patients on average (range, 0-21%)<sup>[63]</sup>. Dvorchik *et al*<sup>[35]</sup> reported a 3.1-fold increased risk of proctocolectomy due to refractory disease in patients with PSC-IBD requiring LT compared with the overall IBD population. Cleveland's study showed that proctocolectomy was performed in 76.5% of patients with PSC-IBD who did not require LT and in 34.9% of those requiring LT (HR = 0.43)<sup>[18]</sup>. IBD activity after LT was assessed through patient perception, clinical assessment, endoscopy, histological findings or some combination therein; these different methods might explain the considerable variability in the reported findings of patients requiring proctocolectomy (0-21%).

The most common surgical option for patients with ulcerative colitis was proctocolectomy with ileal-pouch-anal anastomosis (IPAA). IPAA is relatively safe and effective for patients with IBD receiving LT<sup>[64]</sup>. Pouchitis is the most common complication in patients undergoing IPAA, which can develop in its acute form in up to 66% of patients (14%-66%) and in its chronic form in up to 74% of patients (9%-74%)<sup>[65,66]</sup>. PSC is



related to an increased risk for developing pouchitis; it occurs in 60%-90% of non-transplanted patients with PSC/IBD. The severity of PSC is not related to the risk of pouchitis<sup>[18]</sup>. Whether LT itself significantly modifies the risk of developing pouchitis has not been explored<sup>[18]</sup>. In most series, pouchitis is effectively treated using standard treatment options according to IBD guidelines<sup>[30]</sup>.

The optimal timing for proctocolectomy (before, during or after LT) is not well defined. Pre- and peri-transplant proctocolectomies are significantly protective against recurrent PSC compared with post-transplant proctocolectomy (HR = 0.08) or no proctocolectomy (HR = 0.11)<sup>[39,67]</sup>. Mortality rates up to 26% are reported in patients with cirrhosis who undergo any type of colorectal surgery, with the highest risk among those undergoing emergent procedures<sup>[68,69]</sup>. Abdominal colectomy with IPAA is a technically complex procedure with a high complication rate (up to 52.3%), especially among patients with end-stage liver disease<sup>[70]</sup>. Decisions should be made on an individual basis by team of internists and surgeons with expertise in IBD and liver diseases, keeping in mind the severity of the liver disease, the previous response to therapy, comorbidities and risk of colonic malignant disease.

## COLORECTAL CARCINOMA

The relative risk of colorectal carcinoma (CRC) for all patients undergoing LT compared with age- and sex-matched controls in the general population is 2.8 times higher<sup>[71-73]</sup>. The rates of CRC in patients who undergo LT because of PSC varies from 0-31.5 per 1000 person/year, whereas in patients receiving LT without PSC it is up to 30 times lower (1.3 per 1000 person/year)<sup>[33,37,38,40,74-80]</sup>. Patients with PSC/IBD whose colon is intact at the time of LT experience the highest rates of CRC (0-43.5 per 1000 person/year). An analysis of the National Institute of Diabetes and Digestive and Kidney Diseases' liver transplantation database which includes 798 patients who underwent LT demonstrated cumulative incidence of CRC at 10 years after LT; 11.8% for PSC/IBD, 2.6% for LT unrelated to PSC and 2.8% for LT in PSC without IBD, respectively<sup>[35,78]</sup>. Singh *et al*<sup>[81]</sup> meta-analysis of the pooled incidence rate of *de novo* CRC after LT was 5.8 per 1000 person-years for PSC and 13.5 per 1000 person-years for patients with PSC-IBD and intact colon. Hence, the risk of CRC is approximately 4-fold higher for patients with PSC undergoing LT vs average patients undergoing LT and more than 10-fold higher than patients with PSC/IBD with an intact colon undergoing LT. Because the relative risk of *de novo* CRC after LT for non-PSC indications was estimated as 1.8 times higher than the risk for the general population, the risk of *de novo* CRC for a subset of patients with PSC-IBD and an intact colon can be extrapolated as up to 20-fold higher than the risk for the general population<sup>[81]</sup>.

The risk factors for CRC after LT for patients with PSC are complex, and it is unclear whether transplant-related immunosuppression modifies the risk of CRC after LT. As in the overall population, the risk factors of CRC for patients who undergo LT are the duration of IBD (> 10 years), extension for colonic disease and (in transplanted patients) a longer time period after LT<sup>[63,75,79,80]</sup>. Patient age at the time of IBD diagnosis or LT and IBD activity are not established CRC risk factors<sup>[35,75,80]</sup>. In patients with PSC/IBD, CRC more frequently affects the right side of the colon before and after LT, and this disease is typically localised in the caecum and ascending colon<sup>[77]</sup>. The right colon might be more affected because of the hydrophobic and cytotoxic effects of biliary acid on the colonic mucosa<sup>[82]</sup>.

Endoscopic surveillance with chromendoscopy and serial biopsies of any suspected lesion is recommended for all patients with IBD/PSC after LT. Colonoscopy should be performed annually<sup>[23]</sup>. Proctocolectomy is recommended in case of neoplasia of colonic mucosa.

## PSC AFTER LIVER TRANSPLANTATION

The overall patient and graft 5-year survival rates in PSC recipients are excellent: 95.4% and 89.6%, respectively<sup>[83]</sup>. Patients receiving transplants for PSC have disease-specific complications (excluding the usual post-transplant complications) that might lead to increased morbidity and mortality rates. The most common cause of death remains infection (rates up to 26%). The incidence of acute cellular rejection is higher for patients with PSC and comorbid IBD, increasing the risk<sup>[84]</sup>. PSC recurrence occurs in 20%-50% of liver recipients 5-10 years after LT, and can effect graft and patient survival<sup>[85]</sup>. Only approximately one-third of patients with recurrence develop progressive disease leading to retransplantation or death. The risk factors for recurrence, particularly the influence of the immunosuppressive regimen, remain incompletely understood, however a variety of risk factors have been reported in various series including age, sex mismatch, male sex, coexistent IBD, the presence of an intact colon after transplantation, cytomegalovirus (CMV) infection, recurrent acute cellular rejection, steroid-resistant cellular rejection, the use of OKT3, the presence of cholangiocarcinoma before transplantation, the use of extended donor criteria, and the prolonged use of glucocorticoids<sup>[31,67,86,87]</sup>. However, IBD alone does not adversely affect patient survival after LT, and the risk of recurrent PSC in the allograft might be higher among patients with IBD and an intact colon at LT.

The diagnosis of recurrent PSC after LT is difficult to establish because of the similar effects of compromised hepatic arterial blood flow, chronic/ductopenic rejection, donor/recipient ABO incompatibility, preservation-reperfusion injury, Roux-en-Y-related cholangitis and anastomotic stricture(s) on laboratory, morphological and histological findings. However, IBD is observed

**Table 2 Primary sclerosing cholangitis/inflammatory bowel disease patients proposed management approach in peri-transplant period**

Before LT	Adequate treatment of IBD in order to achieve remission Annual colonoscopic surveillance screening for neoplasia Reconsidering colectomy in patients with refractory disease and neoplasia Screen donor and recipient for CMV antibodies
Preoperative	Clinical remission and cessation of smoking are important in order to reduce the risk of flare up after LT Consider of pre-emptive/continuation of use of 5-ASA to prevent relapse of IBD Consider high risk patients for CMV disease for valganciclovir prophylaxis
Post-transplant	Reconsider risk of rejection and possibility of substituting Tac with CsA in selective patients Avoid MMF due to possible gastrointestinal side effects Reconsider treatment with AzA in recurrence of IBD Reconsider anti-TNF-alfa in refractory IBD Carefully monitor for infections, autoimmune diseases and malignancy Annual colonoscopic surveillance for neoplasia Reconsidering colectomy in patients with refractory disease and neoplasia Treat chronic refractory pouchitis according to standard guidelines Perform surveillance for recurrent PSC especially in recipients with intact colon at LT Screen high risk patients for CMV viremia Positive CMV patients treat with valganciclovir or ganciclovir Perform surveillance for graft rejection and/or vascular thrombosis in patients with active IBD

LT: Liver transplant; IBD: Inflammatory bowel disease; CMV: Citomegalovirus; Tac: Tacrolimus; CsA: Cyclosporine; AZA: Azathioprine; MMF: Mycophenolate mofetil; TNF: Tumor necrosis factor.

more frequently in patients with recurrent disease. Overall short- and medium-term graft and patient survival rates appear to be comparable among patients with PSC/IBD and PSC alone<sup>[38]</sup>. The incidence of hepatic artery thrombosis might be higher in patients with PSC/IBD, especially those with active IBD<sup>[38]</sup>. Concomitant IBD has also been associated with a higher rate of acute cellular and chronic ductopenic rejection, higher risk of graft failure and the need for retransplantation, thereby making early accurate diagnosis and the close monitoring of this disease entity important<sup>[84,88]</sup>. The natural history of recurrent disease varies, and no specific treatment options are recommended<sup>[50,89]</sup>.

## MANAGEMENT OF GRAFT REJECTION AFTER LIVER TRANSPLANTATION

Because a higher rate of rejection complications occur among patients with PSC receiving LT, it is important to reconsider immunosuppressive therapies based on the most potent anti-rejection drugs. In the LT setting, tacrolimus-based anti-rejection therapy has been superior to cyclosporine-based strategies to significantly reduce the risk of acute rejection, steroid-resistant rejection and the risk of graft loss. For every 100 patients receiving LT treated with tacrolimus instead of cyclosporine, rejection and graft loss can be avoided in 9 and 5 patients, respectively<sup>[90]</sup>. Taking the lower risk of acute rejection and steroid-resistant rejection as well as the lower risk of graft loss in patients with tacrolimus treatment into account, a switch to cyclosporine among patients with IBD receiving LT cannot be universally recommended and should be based on individual risk assessments for rejection and the effects on the course of IBD<sup>[47]</sup>.

As in all other transplanted patients, established acute cellular rejection is treated with boluses of corticosteroids<sup>[45]</sup>.

## CONCLUSION

Despite considerable cumulative experience regarding LT for cases of PSC, controversy concerning the course of IBD after LT among these patients is fuelled by the complexity of the IBD/PSC syndrome and small sample size of patient cohorts available for analysis. General guidelines are lacking, and most of the recommended procedures derive from published experiences of uncontrolled studies (Table 2).

PSC is comorbid with IBD in approximately 70% of patients, with UC being the most common type of IBD identified. The number of LT recipients with PSC and AIH is constantly increasing because of the increased number of newly diagnosed patients, inadequate treatment options for prevention of end stage liver disease and the increased availability of organ donors. Excluding cases of on-going IBD, *de novo* IBD has been reported after solid organ transplantation, with an estimated incidence that is ten times higher than the expected incidence of IBD in the general population.

Active IBD at LT is commonly associated with a higher risk of unfavourable IBD disease progression and the onset of other complications (mainly infections, colorectal cancer, acute and chronic graft rejection, hepatic artery thrombosis and PSC recurrence). Currently, no specific guidelines exist for the medical management of patients with PSC/IBD and active IBD before LT. Further studies are suggested in order to improve management of patients with IBD undergoing LT, with emphasis on achieving remission of IBD before the procedure, as well as adequate CRC surveillance

and timely proctocolectomy in selected patients with medically refractory IBD or high risk of CRC. PSC/IBD transplant candidates should be treated similar to other patients with IBD according to general guidelines with special attention placed on the higher risk of immunomodulatory therapy side effects in cases of advanced liver disease and proximate re-evaluation before the patient reaches the top of the transplant list. The introduction of any immunomodulatory therapies in cases of PSC/IBD should be weighed against risk of liver or infectious disease deterioration. Attempts to minimise immunomodulatory therapy in stable patients at the top of the transplant list to reduce the chance of an opportunistic infection should be individually and carefully weighed against the potential for disease flare. The preoperative discontinuation of 5-ASA, smoking and CMV infection also negatively affect post-transplant manifestations of IBD. This result emphasises the importance of proper IBD treatment before transplantation, the early recognition and intervention of infections (*e.g.*, CMV and *Clostridium difficile*), and the continuation of 5-ASA during the peri- and post-operative periods.

The course of IBD in an LT setting is highly variable. Previous studies have shown a deterioration of IBD course in up to 50% of patients, with 30% of patients experiencing repetitive flare-ups and 35% of cases leading to proctocolectomy. Comparing to IBD patients without LT, need for surgery in acute IBD refractory to medical therapy is 3 times more common (nearly 9%).

IBD management among LT recipients represents a therapeutic challenge because of intermittent flare-ups and IBD remissions as well as other possible comorbidities in the LT population (especially infections) and contradictory effects regarding the two strategies applied for immunomodulatory therapy aimed at anti-rejection and IBD flare-up prevention. Patients should be carefully evaluated and treated for other IBD flare-up risk factors (*e.g.*, *Clostridium difficile*, CMV and enteropathogenic infection). The screening and treatment of CMV disease is important not only for preventing *de novo* IBD after LT but also given the risk of PSC recurrence. Because of the overall scarce amount of data, no guideline-based recommendations exist concerning the specific treatment of patients with PSC/IBD during the post-transplant period. IBD treatment strategies seeking to achieve and maintain remission in patients receiving LT are the same for overall IBD population. These strategies include 5-ASA, corticosteroids, azathioprine, and biological therapy. Several facts must be considered when choosing an optimal treatment approach, including drug potency and safety profiles (especially interactions with other immunosuppressants), previous response to therapy in cases of IBD relapse and comorbidities (especially infections and neoplasia). Although the evidence for anti-TNF-alpha application is limited, it might be a safe and effective option for active disease resistance to immunomodulator therapy. However, it is important to

implement more careful surveillance regarding the risk of infectious, autoimmune diseases, and neoplasms with regard to concomitant anti-rejection therapy. Because the principal immunosuppressive agent in LT, tacrolimus, is associated with a four-fold higher risk of post-transplant IBD relapse and MMF as well as GI side effects such as diarrhoea, the substitution of this agents with cyclosporine and azathioprine, drugs with known positive effects on IBD and rejection in solid organ transplantation, is worth considering. Decisions regarding optimal immunosuppressive drugs should be performed on an individual basis because patients with PSC are at a higher risk of acute and chronic graft rejection. When deciding treatments for individual patients with PSC/IBD, it is important to consider the risk of active treatment-resistant IBD occurrence (which is related to an increased risk of colon neoplasia, PSC recurrence, hepatic artery thrombosis, *etc.*) in addition to the potentially increased risk of graft rejection for non-tacrolimus based regimens.

In patients with active IBD and those with intact colons at the time of LT and PSC recurrence, it is important to perform surveillance for graft rejection vascular thrombosis. The risk of CRC is approximately 4-fold higher for patients with PSC who undergo LT vs the average LT recipient and more than 10-fold higher for patients with PSC/IBD with an intact colon. In patients with PSC without known UC screening colonoscopy, multiple rectal biopsies should be performed at the time of diagnosis. If negative, then these biopsies should be repeated every 5 years thereafter because many of these patients are asymptomatic. Patients with PSC and known UC should have colonoscopies during their initial evaluations and every 1-2 years thereafter (before and after LT) because of the increased risk of neoplasia.

Proctocolectomy should be considered in cases of acute severe, medically refractory colitis and dysplasia or colorectal carcinoma. Proctocolectomy with IPAA is feasible and safe at dedicated surgical centres. The optimal timings of pre-, peri-, and post-transplant are not well defined. In selected patients with IBD/PSC and CRC, the risk factors associated with pre-transplant proctocolectomy might represent a successful management strategy in the prevention of CRC and PSC recurrence.

Since most quality data from controlled studies is missing, in order to make final conclusions and specific guidelines for PSC/IBD transplanted patients, we need prospective studies on higher number of patients (stratified for risk factors, type and severity of IBD, PSC and rejection) randomised to treatment with different immunosuppressive protocols.

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