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Alimentary Tract

Effectiveness and safety of anti-TNF therapy for inflammatory bowel disease in liver transplant recipients for primary sclerosing cholangitis: A nationwide case series

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ABSTRACT

Background: There is a lack of consensus regarding the treatment of inflammatory bowel disease (IBD) after liver transplantation (LT) forprimary sclerosing cholangitis (PSC).
Aim: To investigate the safety and effectiveness of anti-TNF therapy in patients with IBD after a LT for PSC.
Methods: We reviewed the medical files of all of the IBD patients who underwent a LT for PSC and who were treated with anti-TNF therapy at 23 French liver transplantation centers between 1989 and 2012.
Results: Eighteen patients (12 with ulcerative colitis and 6 who had Crohn's disease) were recruited at 9 LT centers. All of these patients received infliximab or adalimumab following their LT, and the median duration of their anti-TNF treatment was 10.4 months. The most frequent concomitant immunosuppressive treatment comprised a combination of tacrolimus and corticosteroids. Following anti-TNF therapy induction, a clinical response was seen in 16/18 patients (89%) and clinical remission in 10 (56%). At the end of the anti-TNF treatment or at the last follow-up examination (the median follow-up was 20.9 months), a clinical response was achieved in 12 patients (67%) and clinical remission in 7 (39%). A significant endoscopic improvement was observed in 9 out of 14 patients and a complete mucosal healing in 3 out of 14 patients (21%). Six patients experienced a severe infection. These were due to cholangitis, cytomegalovirus (CMV) infection, *Clostridium difficile*, cryptosporidiosis, or *Enterococcus faecalis*. Three patients developed colorectal cancer after LT, and two patients died during the follow-up period.
Conclusions: Anti-TNF therapy proved to be effective for treating IBD after LT for PSC. However, as 17% of the patients developed colorectal cancer during the follow-up, colonoscopic annual surveillance is recommended after LT, as specified in the current guidelines.

1. Introduction

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by an inflammatory and fibrosing disease of the intra- and/or extra-hepatic bile ducts [1]. A liver transplant (LT) is

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the only curative treatment. More than half of the individuals suffering from this condition are candidates for a LT 10–15 years after PSC diagnosis [2]. In France, PSC currently accounts for approximately 2.5% of the indications for LT [3]. The prevalence of PSC ranges from 0.7% to 5.4% in ulcerative colitis (UC), and from 1.2% to 3.4 in Crohn's disease (CD) [4]. Despite the post-LT immunosuppressive therapy, IBD can develop after a LT, and the activity of pre-existing IBD can worsen, particularly when the treatment with corticosteroids is stopped [5,6]. It is estimated that 14% to 30% of patients with PSC develop de novo IBD 10 years after a LT [7].

There is a lack of consensus regarding the treatment of IBD after a LT for PSC, and the management of these patients remains a challenge at our clinical practice. The main reason for avoiding the use of biologics with these patients is that this involves the use of multiple associated immunosuppressive treatments, with the potential for an increased risk of serious infections, including opportunistic infections [8].

IBD associated with PSC has a higher risk of colorectal cancer (CRC) than other forms of IBD and it consequently requires annual colonoscopic surveillance, as recommended by international guidelines. Since CRC with IBD is driven by chronic inflammation, macro- and microscopic inflammation should be maintained within optimal levels. In some cases, anti-TNF therapy is required to induce and maintain clinical and endoscopic remission in patients who are resistant to or are unable to tolerate other immunosuppressants. There is scant data regarding the use of biologics to treat IBD in PSC patient populations after LT, and no definite conclusions can be drawn from the available evidence due to the small sample sizes [9–14]. A recent systematic review and meta-analysis concluded that further studies are needed to confirm the safety of anti-TNF therapy in post-transplant patients [15].

The main aim of this study was to investigate the efficacy and safety profile of anti-TNF therapy in patients with IBD after a LT for PSC.

2. Materials and methods

This was a retrospective, multicenter, nationwide study. The 23 liver transplantation centers in France were asked to identify adults who underwent a LT for PSC between the 1st of January 1989 and the 31st of December 2012, and which of these patients subsequently received any anti-TNF therapy. The inclusion date was defined by the date of the first anti-TNF administration after the LT.

The following information was collected through a retrospective review of the medical files: the type and the history of the IBD, all of the IBD-related medications provided prior to and following the LT, the PSC history, the LT indication (e.g. septic complication or secondary biliary cirrhosis), the rejection episode, whether it involved a cytomegalovirus (CMV) infection, and all of the immunosuppressive treatments provided after the LT. All of the adverse events that occurred after anti-TNF initiation in the post-LT setting were collected and classified by type (e.g. infectious, neoplastic, immune dysfunction, allergic, or other).

The efficacy of the anti-TNF therapy as induction therapy (i.e. within the three months following the initiation of the anti-TNF treatment) and as maintenance therapy until the end of the treatment or at the most recent follow-up was extracted from the medical files. A clinical response was defined as an improvement in digestive symptoms (e.g. a decrease or normalization of the number of bowel movements, and a decrease or disappearance of abdominal pain and bloody mucosal discharges) as assessed by a physician, and classified as either a partial clinical response or as a clinical remission depending on whether the digestive symptomatology fully disappeared. Primary failure was defined as the absence of any IBD clinical improvement during the anti-TNF induction therapy. Secondary failure was defined as a clinical deterioration after a period of improvement in patients receiving anti-TNF maintenance therapy.

Table 1
Data regarding the IBD prior to anti-TNF initiation after LT.

	$n = 18$
UC	12 (67%)
Of which E3[a] extension	10 (83%)
Pouchitis in colectomized patients	2 (17%)
Crohn's disease	6 (33%)
Localization and phenotype[a]	
L1	0
L2	2 (33%)
L3	4 (67%)
L4	2 (33%)
B1	5 (83%)
B2	1 (17%)
B3	0
p	1 (17%)
De novo IBD	4 (22%)
IBD diagnosed prior to the LT	14 (78%)
Activity of the IBD on the day of the LT (N = 14)	
None or minimal	8 (57%)
Moderate	5 (36%)
Severe	1 (7%)
Median duration of the progression of the IBD before anti-TNF initiation (years)	14.1 (0.4–27.6)
Median delay between LT and anti-TNF initiation (years)	5.9 (1.1–20.8)
Median delay between start of the flare-up and anti-TNF initiation (months)	5.2 (1.1–33.6)

[a] According to the classification of Montreal.

The endoscopic response was also assessed, when the relevant information was available, by comparing endoscopic findings before the start of the anti-TNF treatment and the most recent available endoscopic evaluation. The endoscopic response was classified as either no response, partial, or complete mucosal healing. No endoscopic response was defined as a lack of improvement or a worsening of the endoscopic lesions. For patients with CD, complete mucosal healing corresponded with disappearance of all of the mucosal ulcerations; whereas for patients with UC, a Mayo endoscopic subscore less than or equal to 1 was required. A partial endoscopic response was defined as an improvement in the endoscopic lesions without mucosal healing. This was a retrospective and multicenter study, such that the endoscopic follow-up was performed at the discretion of each hepato-gastroenterology team. The end of the treatment was defined as the date on which the anti-TNF treatment was stopped or the most recent follow-up when anti-TNF treatment was still ongoing. Data collection took place until the 15th of July 2014. Due to the small sample size, we used only descriptive statistics.

Descriptive statistics were reported as numbers (percentage), ranges, and medians as appropriate.

3. Results

3.1. Efficacy of the anti-TNF therapy

Between the 1st of January 1989 and the 31st of December 2012, 518 LTs were performed in France for PSC. Nine French LT centers responded to our survey, allowing for inclusion of 18 patients (14 men), with a median age of 26.4 years at the time of their LT. The baseline characteristics of the 18 included patients are shown in Tables 1–3. One patient was transplanted in 1989, while for all of the remaining patients the LT was performed between 1997 and 2012. The indication for the LT was a septic complication (recurrent cholangitis) for 5 patients (28%), secondary biliary cirrhosis for 6 (33%), and both of these indications for 7 patients (39%). The initial immunosuppressive treatment comprised a combination of

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