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Anti-TNFα treatment in children and adolescents with combined inflammatory bowel disease and autoimmune liver disease

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Abstract

Objectives: Inflammatory bowel disease (IBD) and autoimmune liver disease (AILD) are closely associated, the former often dictating progression of the latter. Antibodies to tumor necrosis factor alpha (anti- TNFα) are effective in the management of IBD, but may cause liver injury.

Methods: Retrospective review of medical records of patients with juvenile AILD who received anti-TNFα for IBD to evaluate the safety and efficacy of anti-TNFα.

Results: Eleven patients (6 males), aged 9-15y (median 13y) were identified. 10 had ulcerative colitis (UC) and 1 Crohn's disease; 2 had autoimmune hepatitis type 1 (AIH-1) and 9 autoimmune hepatitis-sclerosing cholangitis variant. All patients were started on infliximab (5mg/kg) and 2 required dose increase (10mg/kg); 3/11 switched to adalimumab due to allergic reaction or non-response. 3 received adalimumab after losing response or developing antibodies to IFX. Liver function tests (LFTs) improved in 5, 1 continued to have stably abnormal LFTs and 2 maintained normal LFTs. Patients on adalimumab showed stable or improved liver function compared to pre-treatment status. 6/8 treated with a full course of infliximab maintained clinical remission of IBD for 6m-2.5y; of the 6 patients treated with adalimumab, one sustained IBD clinical remission for 24 months, 2 achieved remission only after tacrolimus addition and 3 did not respond.

Conclusions: IBD in patients with AILD can be aggressive, requiring escalation to anti-TNFα or switching to other biologics. In this series, anti-TNFα did not impair liver function and improved gut disease in most of the patients, indicating that it can be beneficial and safe.

Keywords: infliximab; adalimumab; liver injury

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What is known

- Inflammatory bowel disease (IBD) and autoimmune liver disease (AILD) are closely associated
- Antibodies against tumor necrosis factor α (TNFα) have been associated with drug induced liver injury

What is new

- Children and adolescents with AILD may have difficult to control IBD
- Anti-TNFα therapy can be beneficial for children and adolescents with IBD and combined AILD without worsening the liver function

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Introduction

The association between inflammatory bowel disease (IBD) and hepatobiliary disease was recognized in the 19th century [1],[2]. Since then many theories have been proposed to explain this link [3, 4]. The underlying pathophysiological mechanisms for the development of IBD have not yet been clarified, however emerging evidence has revealed a key role for tumor necrosis factor α (TNFα) [5][6]. Interestingly, in untreated children with autoimmune hepatitis type 1 (AIH-1) the level of TNFα is elevated compared to healthy controls [7]. Moreover, an association has been identified between the polymorphism at position 308 in a promoter region of TNFα and the severity of AIH-1 [8]. In a mouse model of AIH it was shown that TNFα is essential for the development of hepatitis, being critically involved in its induction through upregulation of hepatic CCL20 expression [9]. These observations suggest that TNFα could be also implicated in the pathogenesis of autoimmune liver disease (AILD), shedding some light to the close relationship between IBD and AILD.

Over the past 15 years anti-TNFα biotherapies, such as infliximab and adalimumab, have revolutionized the treatment of several immune-mediated diseases and have dramatically influenced the outcome of patients with refractory IBD [10, 11]. Increasing experience with anti-TNFα agents has proven their safety and efficacy [11, 12, 13], but a number of other reports indicate a risk for drug-induced liver injury [14-16]. Infliximab has been recently assigned to category A in the categorization of drugs implicated in causing liver injury. This association has been addressed in more than 100 cases in the published literature [17]. It is postulated that hepatotoxicity can be idiosyncratic, mediated by an aberrant immune response induced by blocking TNF in

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susceptible hosts [18] or as inferred from the appearance of ANA, SMA and anti-double-stranded DNA antibodies in some cases [19, 20]. One of the proposed mechanisms for the induction of ANA is the ability of infliximab to induce cell apoptosis through binding transmembrane TNFα on the cell surface and thus provoking the release of nucleosome [20]. Cholestasis [21], but most commonly, autoimmune hepatitis have been also related to the use of adalimumab [22, 23].

While there are a few conflicting reports of anti-TNFα treatment in adult patients with liver disease [24-26], the safety profile of anti-TNFα treatment in the pediatric population with combined IBD and chronic liver disease is largely unknown and represents a clinical challenge.

Patients and methods

A medical record search was performed to identify pediatric patients with IBD and AILD who received anti-TNFα therapy between 2009- 2015 in our Centre. The type of IBD and AILD, age at diagnosis, concomitant treatment and anti-TNFα agent used in each patient were recorded. Patients had their liver function tests (LFTs) tested before biologic treatment, three and twelve months into treatment. Monitoring of the liver function continued 3-monthly when treatment escalation with increased doses of anti-TNFα was required. IBD activity was monitored 3-monthly with inflammatory markers (CRP), faecal calprotectin (FC) and repeat endoscopy when indicated. In accordance with European regulation, approval of IRB was not obtained, as this is an observational study without any additional therapy or monitoring procedure.

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Results

Sixty- one patients with IBD and AILD were identified, eleven (6 males, 5 females) of whom (aged 9-15 years, median 13y) received anti-TNFα treatment. Two had AIH-1 and nine autoimmune hepatitis-sclerosing cholangitis (AIH-SC) variant. All were anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic (ANCA) and/or anti-smooth muscle antibody (SMA) positive. 8/11 had elevated IgG (16.9- 38.29g/L, median 25.6g/L, reference range 5.4-16.1g/L) at diagnosis. All had undergone endoscopies and were diagnosed with histologically proven IBD. The distribution of the bowel inflammation at diagnosis is shown in table 1. Liver disease was confirmed by liver biopsy and magnetic resonance cholangiography (MRCP) in all patients and was treated with standard prednisolone/azathioprine combination (3). At the time of starting anti-TNFα treatment, patients were on oral prednisolone (5-20mg/day), azathioprine (50-150mg/day), mycophenolate mofetil (MMF) (750mg twice daily), tacrolimus (1.5-3mg/day), ursodeoxycholic acid (UDCA) (10mg/kg BD). Patients' demographic and clinical data are shown in Table 2.

Anti-TNFα therapy was commenced because of unsuccessful treatment of IBD with 5-ASA (1.2- 4g/day) and other immunosuppressive agents (table 2). The median time for the initiation of anti-TNFα treatment after the diagnosis of IBD was 2 years and 1 month (2 months- 4.5y). All eleven patients were started on IV IFX (5mg/kg), the treatment schedule consisting of induction at weeks 0, 2 and 6, followed by eight-weekly infusions. Patient 6 and 7 followed this treatment regime for 6 months and then received 6-weekly infusions. Patient 6 achieved good control of his colitic symptoms. In patient 7

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there was no clinical improvement and the trough level of IFX was reported sub-therapeutic (1ug/ml). The plan is for the dose of IFX to be increased to 10mg/kg 6-weekly.

Patients 9, 10 and 11 stopped IFX after 1-3 doses because of allergic reactions or no response. These three patients, who did not undergo the full course of IFX, were switched to adalimumab 40mg subcutaneously two-weekly, after induction with one dose of 80mg. Patient 9 had established portal hypertension when commenced on biologics. She did not respond to IFX and was treated with Adalimumab for 24 months. Her GI symptoms persisted and she was transitioned to the adult service and was treated with newer biologics (golimumab and vedolizumab). Her severe portal hypertension has made the option of colectomy very challenging and the patient is due to undergo a transjugular intrahepatic portosystemic shunt (TIPS) procedure with a view to reduce her portal pressure to enable proctocolectomy. Patient 10 developed a reaction (vomiting, pre-fainting episode) during the first infusion of IFX and IFX was discontinued. He was treated with Adalimumab for 11 months, but was then was lost to follow up. When adalimumab was restarted, he developed antibodies within a month. IFX therapy was reconsidered, but during the second infusion, he developed a severe anaphylactic reaction. The adult GI services took over his care and he was commenced on vedolizumab. His UC is in clinical remission and transaminase levels are normal. GGT levels remain raised (135 IU/L). Patient 11, with difficult to control panenteric Crohn's disease, was started on IFX 2 months after the diagnosis of IBD. Shortly after he was found to be cytomegalovirus viraemic and he received valganciclovir for 6 weeks. A second dose of IFX, 7 weeks later, did not result in clinical or biochemical improvement.

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An extensive immunologic work-up was negative. He commenced adalimumab, but only after the introduction of tacrolimus 3 weeks later, his symptoms resolved. Azathioprine was also substituted by methotrexate (15mg s/c weekly).

Three patients (patient 1, 3 and 8) developed antibodies to IFX. Patient 1 has been treated with Adalimumab for 8 months (40mg 2 weekly for 5 months and 60mg 2 weekly for 3 months). Patient 3 developed antibodies to IFX 20 months into treatment and in view of the quiescent colitis on repeat ileocolonoscopy, she hasn't been started on an alternative biologic agent. Patient 8 developed low titer antibodies 10 months into treatment with IFX. Repeat endoscopy showed histologic improvement with moderate chronic pan-proctocolitis. The trough level and antibody titer of IFX will be repeated before a decision to discontinue treatment is made.

A further two patients (patient 4 and 5) lost response to IFX. Patient 4 required introduction of Tacrolimus (5mg daily, trough 7-10) in addition to adalimumab for the control of the colitic symptoms. Patient 5 underwent total colectomy 17 m after adalimumab treatment. Repeat liver biopsy post-colectomy showed progression of fibrosis, with only minimal inflammatory activity and his current treatment consists only of UDCA.

Patient 2, a girl with autoimmune hemolytic anemia and autoimmune liver underwent liver transplantation for AIH- SC variant in our Centre. Her LFTs remained persistently deranged post-surgery. A year after transplantation she was diagnosed with UC and two years post-transplantation she was commenced on IFX. Her immunosuppression therapy remained unchanged and following IFX induction, LFTs normalized. Repeat endoscopy and liver biopsy at one year on anti-TNFα treatment

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showed persistent chronic inflammation in the gut and chronic, diffuse cholangiopathy in the liver, also confirmed by MRCP. The hepatic artery on ultrasound scan was normal. 2.5 years into treatment with IFX she underwent MRCP that showed mild improvement of the bile duct damage and stricturing of the proximal ducts; GI endoscopy revealed persistently active UC. IFX dose was increased to 10mg/kg eight- weekly and after two infusion of higher dose IFX, LFTs improved, CRP normalized and colitic symptoms resolved. Over a 3-year follow-up period on IFX treatment, no significant infections, EBV/CMV viremia or evidence of graft rejection have occurred.

Median follow- up from starting treatment with biologics is 20 months (range 10m-3y). LFTs before and during IFX are shown in figure 1 and before and during adalimumab in figure 2. Table 3 shows the duration of IFX and adalimumab treatment for each patient.

Discussion

Our series shows that patients with juvenile autoimmune liver disease and concomitant aggressive IBD can be safely treated with anti-TNFα agents with no deterioration of liver function, the majority showing improvement of IBD symptoms and liver function tests.

In clinical practice, the risk of liver injury induced by anti-TNFα agents must be taken into account especially when these biological therapies are used in patients with combined IBD and chronic liver disease. Among children with autoimmune hepatitis-sclerosing cholangitis variant almost half have concomitant IBD [4], but also AIH can be

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associated with IBD, particularly UC [27]. It has been reported that the co-existence of AIH and UC does not influence adversely treatment outcome [28]. Ordonez et al have suggested that pediatric UC associated with autoimmune diseases is a distinct form of IBD with less aggressive evolution requiring less corticosteroids and immunomodulators than UC without extra intestinal autoimmune manifestations [29]. In contrast, a recent pediatric study shows that the disease activity of IBD is similar irrespective of the presence of sclerosing cholangitis [30]. In our experience, though the majority of children with concomitant AILD and IBD respond to standard immunosuppression, there is a subgroup of patients with severe IBD, in whom the disease is very difficult to control. In these patients, adequate treatment of the colitis is essential as progression of liver damage closely parallels the activity of the intestinal disease [31].

In this retrospective study, anti-TNFα agents were used in 11 children or adolescents with combined AILD and IBD refractory to standard treatment. While nine of them had AIH-SC variant, two had AIH, highlighting the fact that AIH can also be associated to severe IBD. In these difficult-to-treat patients both intestinal and liver diseases are usually progressive, leading to cirrhosis and liver transplantation. Despite their underlying disease, none of these patients developed drug induced liver injury (DILI) even on increased doses of anti-TNFα therapy. Interestingly, patient 2 and 5 showed an improvement of their liver function on 5mg/kg of IFX and a variable rise in LFTs on 10mg/kg. When patient 5 was switched to adalimumab, his LFTs showed further improvement, which persisted even with adalimumab dose escalation (80mg). All patients showed improvement of their intestinal disease for a variable period of time, indicating that this treatment can be beneficial.

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One of our patients with AIH-SC variant developed IBD and recurrent sclerosing cholangitis 1 and 3 years after liver transplantation respectively. She responded satisfactorily to IFX treatment, in agreement with the observation by Sandhu et al, who investigated the safety profile of anti-TNFα therapy for refractory IBD in the post liver transplant population in adults and concluded that it can be safely and effectively used in the majority of cases [32]. Further reports support the safety of IFX therapy in the graft setting [33, 34]. However, long-term studies in a larger number of patients are needed to confirm the safety and efficacy of this treatment option.

A few case reports have suggested that anti-TNFα therapy is an alternative option in controlling difficult-to-treat isolated AIH in adults [35, 36]. In 2012, a retrospective series described the use of IFX in 11 AIH patients who had not achieved remission with standard immunosuppression and other alternative treatments [37]. After 3 infusions of IFX (5 mg/kg at weeks 0, 2 and 6), all patients showed biochemical improvement and five, who had a follow up liver biopsy also showed histological improvement. However, six of the 11 patients developed infectious complications whilst on IFX therapy. In contrast, in the present series of pediatric patients with a median follow up of 20 months (range 10m-3y) after commencing anti-TNFα therapy, we have observed only one mild infectious complication, i.e. asymptomatic cytomegalovirus viraemia after the first administration of IFX, which responded satisfactorily to anti-viral treatment. Following the retrospective study in adults, the off-label use of IFX in a single pediatric patient with AIH refractory to standard immunosuppressive therapy was reported to lead to sustained biochemical response, steroid weaning and removal from the liver transplantation list

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[38]. These reports, together with our observations, suggest that anti-TNFα agents might have a role in selected difficult-to-treat autoimmune liver disease patients.

A limitation of our retrospective study in regards to the effect of anti-TNFα therapy on the underlying liver disease is the lack of follow up liver biopsies and cholangiographic studies in all patients. On the other hand, the major indication for anti-TNFα treatment in our patients was the control of the inflammatory bowel disease. Another limitation of our study is the small number of patients.

In conclusion, anti-TNFα therapy was safe and did not worsen liver function in this single-centre case series of 11 children with AILD and poorly- controlled IBD. While the underlying hepatopathy may have improved on anti- TNFα treatment, prospective multi-centre studies in a large number of patients, including serial examinations of liver histology, are needed to confirm our results.

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Figure 1. Liver function tests before starting infliximab (baseline), after infliximab induction [i.e. at 3 months (3m-IFX)], and after 12 months on infliximab (12-m IFX) in 8 patients treated with a complete course of the drug. For patients 2 and 5, liver function tests are reported also after the infliximab dose was increased to 10mg/kg.

IFX, infliximab; AST, aspartate aminotransferase, normal values 3-35IU/L; ALT, alanine aminotransferase, normal values 5-55IU/L; GGT, gammaglutamyl transpeptidase, normal values 1-55IU/L, bilirubin 3-20µmol/L)

Figure 1

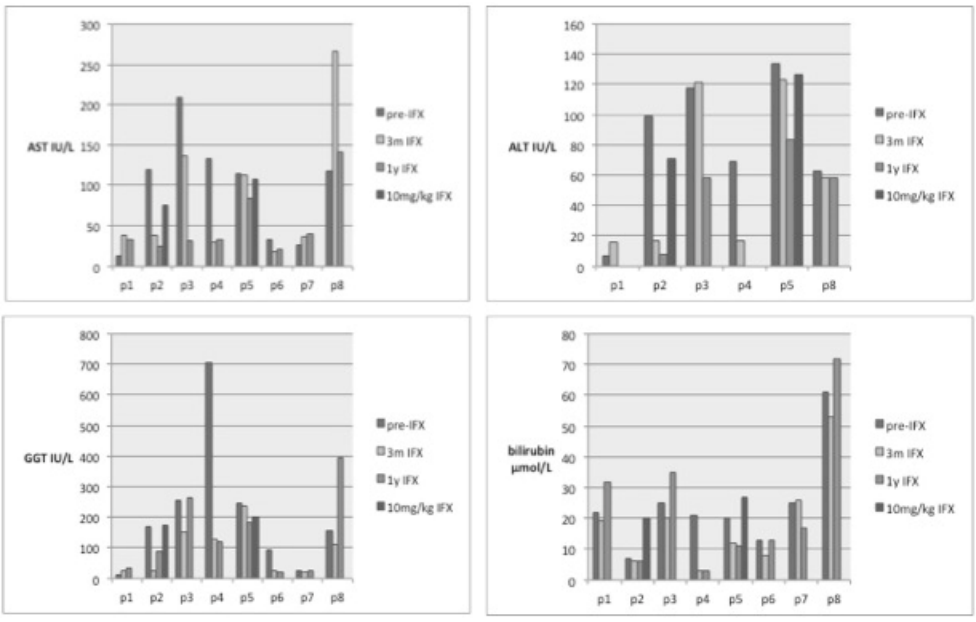

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Figure 2. Liver function tests before starting adalimumab (baseline), after three months of treatment (3m-ADA), and after 12 months of treatment (12-m ADA) in 6 patients. All patients had previously received infliximab: patients 9, 10 and 11 stopped infliximab after 1-3 doses because of allergic reactions or no response; patients 1, 4 and 5 developed antibodies or lost response to infliximab after 1, 3 and 1.5 years of treatment. For patient 5 liver function tests after an increase of the adalimumab dose to 80mg 2-weekly are also reported.

ADA, adalimumab; AST, aspartate aminotransferase, normal values 3-35IU/L; ALT, alanine aminotransferase, normal values 5-55IU/L; GGT, gammaglutamyl transpeptidase, normal values 1-55IU/L, bilirubin 3-20µmol/L)

Figure 2

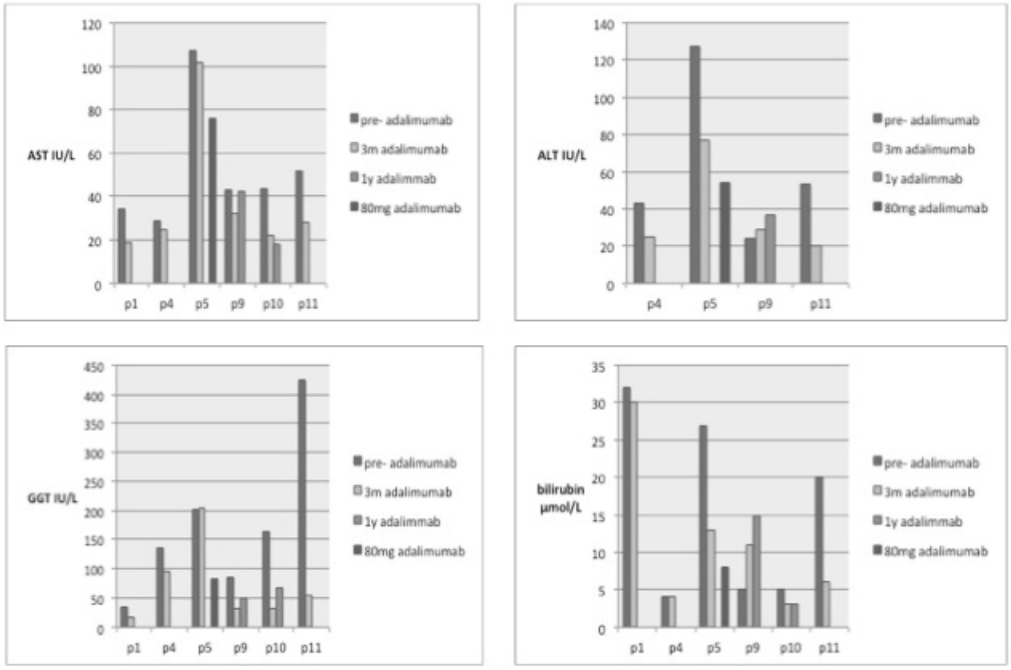

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Table 1. Distribution of bowel inflammation at diagnosis of IBD

	Distribution of gut inflammation
P 1	pancolitis and backwash ileitis
P 2	colo-proctitis
P 3	pancolitis
P 4	pancolitis
P 5	pancolo-proctitis
P 6	distal colitis (rectum, sigmoid, descending colon)
P 7	distal colitis (rectum, sigmoid, descending colon)
P 8	pancolitis
P 9	pancolitis
P 10	pancolitis
P 11	esophagitis, gastritis, duodenitis, ileitis, colitis

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Table 2. Patients' demographic and clinical data

	Sex	Age (years) at diagnosis of AILD/IBD	IBD	AILD	Treatment of AILD & IBD	Age (years) at starting anti-TNFα	Anti-TNFα
Patient 1	F	6/12	UC	AIH-1	Pred, AZA, 5-ASA	16	Infliximab → Adalimumab
Patient 2	F	2/14	UC	Liver Tx, AIH- sclerosing cholangitis variant recurrence	Pred, Tac, MMF, 5-ASA, UDCA	15	Infliximab
Patient 3	F	13/14	UC	AIH- sclerosing cholangitis variant	Pred, Tac, MMF, 5-ASA, UDCA	17	Infliximab
Patient 4	M	12/12	UC	AIH- sclerosing cholangitis variant	Pred, AZA, 5-ASA, UDCA	13	Infliximab → Adalimumab
Patient 5	M	11/11	UC	AIH- sclerosing cholangitis variant	Pred, MMF, 5-ASA, UDCA	12	Infliximab → Adalimumab
Patient 6	M	15/15	UC	AIH- sclerosing cholangitis variant	Pred, MMF, UDCA	17	Infliximab
Patient 7	M	11/9	UC	AIH- sclerosing cholangitis variant	Pred, AZA, 5-ASA, UDCA	11	Infliximab
Patient 8	F	11/11	UC	AIH- sclerosing cholangitis variant	Pred, 5-ASA UDCA	13	Infliximab
Patient 9	F	10/13	UC	AIH-1, PTH	Pred, Tac, 5-ASA, UDCA	13	Infliximab → Adalimumab
Patient 10	M	14/13	UC	AIH- sclerosing cholangitis variant	Pred, AZA, 5-ASA, UDCA	14	Infliximab → Adalimumab
Patient 11	M	14/14	CD	AIH- sclerosing cholangitis variant	Pred, AZA, UDCA	14	Infliximab → Adalimumab

AILD, autoimmune liver disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; AIH-1, autoimmune hepatitis type 1, liver Tx: liver transplantation; PTH, portal hypertension; Pred, prednisolone, AZA, azathioprine; MMF, mycophenolate mofetil; 5-ASA, 5-aminosalicylic acid; UDCA, ursodeoxycholic acid

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Table 3. Duration of anti-TNFα treatment, presence of anti-infliximab (IFX) antibodies and tacrolimus treatment in the 11 patients with autoimmune liver disease and inflammatory bowel disease

	Duration of IFX treatment	Antibodies to IFX	Duration of adalimumab treatment	Introduction of tacrolimus
P1	1y	yes	8m	-
P2	3y	no	-	-
P3	20m	yes	-	-
P4	26m	no	3m	yes
P5	18m	no	17m	-
P6	1y	no	-	-
P7	10m	no	-	-
P8	10m	yes	-	-
P9	3m	no	24m	-
P10	1 infusion	no	12m	-
P11	2 infusions	no	10m	yes

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