# PANCREAS, BILIARY TRACT, AND LIVER

## Effects of Tumor Necrosis Factor Antagonists in Patients With Primary Sclerosing Cholangitis

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**BACKGROUND & AIMS:** **Few patients with primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBDs) are exposed to tumor necrosis factor (TNF) antagonists because of the often mild symptoms of IBD. We assessed the effects of anti-TNF agents on liver function in patients with PSC and IBD, and their efficacy in treatment of IBD.**

*Abbreviations used in this paper:* ALP, alkaline phosphatase; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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**METHODS:** We performed a retrospective analysis of 141 patients with PSC and IBD receiving treatment with anti-TNF agents (infliximab or adalimumab) at 20 sites (mostly tertiary-care centers) in Europe and North America. We collected data on the serum level of alkaline phosphatase (ALP). IBD response was defined as either endoscopic response or, if no endoscopic data were available, clinical response, as determined by the treating clinician or measurements of fecal calprotectin. Remission was defined more stringently as endoscopic mucosal healing. We used linear regression analysis to identify factors associated significantly with level of ALP during anti-TNF therapy.

**RESULTS:** Anti-TNF treatment produced a response of IBD in 48% of patients and remission of IBD in 23%. There was no difference in PSC symptom frequency before or after drug exposure. The most common reasons for anti-TNF discontinuation were primary nonresponse of IBD (17%) and side effects (18%). At 3 months, infliximab-treated patients had a median reduction in serum level of ALP of 4% (interquartile range, reduction of 25% to increase of 19%) compared with a median 15% reduction in ALP in adalimumab-treated patients (interquartile range, reduction of 29% to reduction of 4%; $P = .035$). Factors associated with lower ALP were normal ALP at baseline ($P < .01$), treatment with adalimumab ($P = .090$), and treatment in Europe ($P = .083$).

**CONCLUSIONS:** In a retrospective analysis of 141 patients with PSC and IBD, anti-TNF agents were moderately effective and were not associated with exacerbation of PSC symptoms or specific side effects. Prospective studies are needed to investigate the association between use of adalimumab and reduced serum levels of ALP further.

*Keywords:* Hepatic; Anti-Inflammatory; Intestine; Liver Transplantation.

See editorial on page 2173.

Anti-tumor necrosis factor (TNF) drugs including infliximab and adalimumab are established treatments for inflammatory bowel disease (IBD). Primary sclerosing cholangitis (PSC) is a chronic, inflammatory, cholestatic liver disease of unknown etiology, which may result in cirrhosis and liver transplantation. PSC and IBD are associated closely: the prevalence of IBD in PSC is 60% to 80%. PSC IBD is characterized by quiescent intestinal inflammation, higher prevalence of pancolitis, backwash ileitis, rectal sparing, and increased colorectal cancer risk.[1,2]

Anti-TNF drugs often are not indicated in milder PSC IBD and few studies have reported on anti-TNF treatment in PSC. Whether PSC-IBD patients respond to anti-TNF agents to the same extent as IBD patients without PSC is not known. Whether the presence of PSC puts IBD patients at greater risk of side effects or adverse events during anti-TNF treatment is not elucidated. It has been proposed that there is a pathogenic link between gut inflammation and biliary inflammation, which would suggest that effective treatment for IBD could affect PSC positively. Indeed, colectomy has been associated with reduced PSC recurrence after liver transplantation,[3] although the impact of colectomy for PSC progression and prognosis is controversial.[4,5] It is speculated that IBD inflammation may drive liver inflammation; however, some studies have indicated that more progressive PSC is associated with less active ulcerative colitis.[6] Knowledge of immunologic mechanisms linking IBD and PSC, as well as with a variety of other inflammatory disorders associated with IBD such as spondyloarthritis and skin inflammation, is limited.[7]

### What You Need to Know

#### Background

The authors assessed the effects of tumor necrosis factor (TNF) antagonists (adalimumab or infliximab) in patients with primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD).

#### Findings

In a retrospective analysis of 141 patients with PSC and IBD, the authors observed response of IBD to treatment in 48% and remission of IBD to treatment in 23%, with no specific safety signals. Serum levels of alkaline phosphatase decreased with adalimumab, but not infliximab.

#### Implications for patient care

Anti-TNF agents are effective in the treatment of IBD in patients with PSC, although not as effective as in patients with non-PSC IBD. PSC should not be a contraindication to treatment with anti-TNF agents.

The aim of this study was to evaluate anti-TNF safety and efficacy in PSC IBD and to examine the effect of anti-TNF agents on gut and liver disease in a large population of PSC-IBD patients.

## Methods

### *Patient Recruitment*

A retrospective analysis of PSC-IBD patients receiving their first exposure to anti-TNF as treatment for their IBD

was performed via the International PSC Study group (www.ipscsg.org) (Supplementary Table 1). PSC and IBD diagnoses were confirmed using standard criteria.[8] Patients were included if they had received at least 2 doses of anti-TNF and had baseline blood tests (not >2 months before drug initiation and <7 days after drug initiation). Patients with liver transplantation before anti-TNF initiation were considered separately. A case record form was completed by participating centers and data were analyzed centrally at the Karolinska University Hospital in Stockholm. Patients with insufficient data were excluded, (Figure 1). Ethical approval was obtained locally by participating sites.

### Data Collected

Data collected included sex, weight, height, age at diagnosis of PSC and IBD, IBD characterization and classification, endoscopic data, PSC characteristics, symptoms, type of PSC, the presence of cirrhosis, and drug treatment. Anti-TNF drug treatment schedules were recorded as well as reasons for discontinued treatment and side effects. IBD activity, endoscopic IBD response, and remission were recorded. If sufficient endoscopic data were unavailable, clinical response or remission as determined by the treating clinician was recorded.

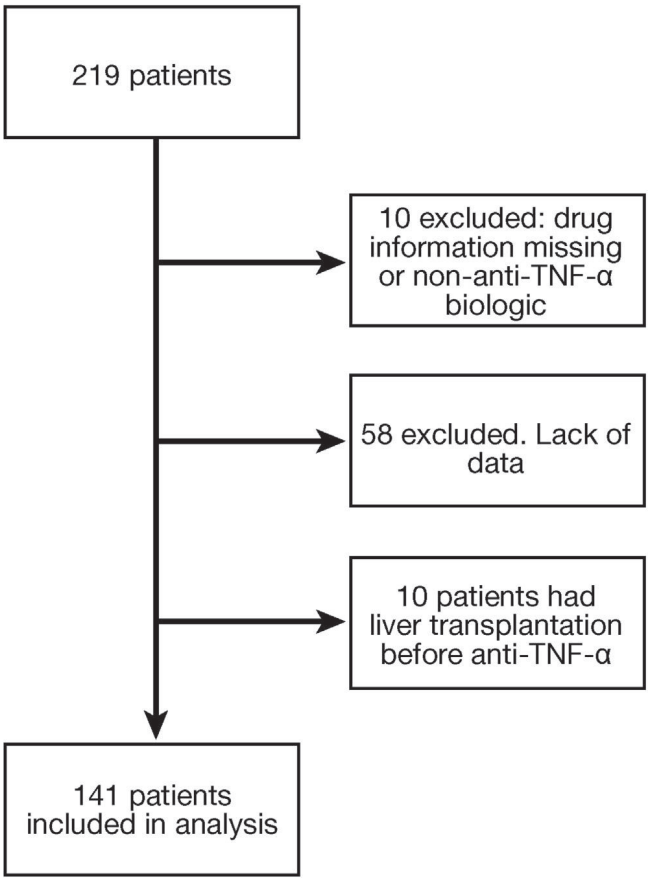


**Figure 1.** Flow diagram of patient exclusion. Patients were excluded if data on type if anti–tumor necrosis factor (TNF) or laboratory data were insufficient. Patients with liver transplantation before initiation of anti-TNF were considered separately.

Laboratory parameters collected before and after treatment (0, 3, 6, and 12 mos) were as follows: blood counts, serum biochemistry (including liver biochemistry), and fecal calprotectin. Patients were included only if they had follow-up bloods during at least 1 of the following time points after baseline: 3 months (blood tests between 6 weeks and 4 months from drug initiation); 6 months (between 5 and 7 months); 12 months (from 10 to 14 months). Blood tests that took place between these time periods were omitted. If there was more than 1 blood test in the relevant interval, the sample taken closest to 3, 6, or 12 months from drug initiation was used. Blood parameters were normalized to the local laboratory normal range and expressed as multiples of the upper limit of normal (×ULN). IBD response was defined as either endoscopic response or, if endoscopic data were not available, clinical response as determined by the treating clinician, or a decrease in fecal calprotectin level of 30% or more from baseline, or absolute value less than 250 $\mu$g/g. Remission was defined more stringently as endoscopic mucosal healing or, if endoscopic data were unavailable, as clinical remission according to the physician's assessment.

### Outcomes

Alkaline phosphatase (ALP) is a recognized surrogate marker for PSC treatment response,[9] and this was used as a marker of PSC progression. In addition, PSC-related outcomes were analyzed including new-onset jaundice, dominant stricture, development of portal hypertension, liver failure, increased pruritus, episodes of recurrent cholangitis, and worsening of abdominal pain.

### Statistical Analyses

Normality was evaluated using Shapiro–Wilk tests and visual assessment of plotted data. Alterations in variables across time were analyzed using the Wilcoxon signed-rank test or the Kruskall–Wallis test. Differences between groups were analyzed using the Mann–Whitney *U* test. Categoric values were compared using chi-squared tests and correlations were assessed with the Spearman rank correlation coefficient. Longitudinal comparison of binary variables was performed using the McNemar test. Multiple linear regression analyses were performed using the backward selection of variables method and non-normally distributed outcomes were natural log transformed. Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY).

## Results

### Study Population

Data were collected on 219 patients from 20 sites in 12 countries in Europe and North America (Supplementary Table 1). Sixty-eight cases were

excluded: 10 cases because the biologic drug used was unknown or was not an anti-TNF, and 58 because of lack of laboratory data (eg, no baseline ALP level available). The 10 patients who underwent liver transplantation before receiving anti-TNF were considered separately (Figure 1).

Thus, 141 non–liver transplanted patients were included in the main analysis (Table 1). Of these, 59 (42%) were treated with ursodeoxycholic acid (UDCA) at baseline, and 72 (51%) were not (in 10 [10%], UDCA data were not available). Of those patients who started anti-TNF while on UDCA, all but 4 remained on UDCA for the whole first year. Of those patients not taking UDCA at baseline, only 8 started UDCA during the first year.

### *Inflammatory Bowel Disease Response*

Data on IBD response at 3 months were available for 104 patients. Fifty (48%) were deemed to have responded to anti-TNF, 48 (46%) were nonresponders, and 6 (6%) had discontinued anti-TNF. Remission at 3 months

**Table 1.** Demographic Factors at Baseline of 141 Nontransplanted Patients Included in the Main Analysis

| Demographic factor | Infliximab, n = 110 | Adalimumab, n = 31 | Total, n = 141 | *P* value |
|---|---|---|---|---|
| Male, n (%) | 71 (65) | 18 (58) | 89 (63) | .550 |
| Age at IBD diagnosis, *y*, median (IQR) | 19 (15–30) | 21 (14–28) | 20 (15–30) n = 137 | .983 |
| Age at PSC diagnosis, *y*, median (IQR) | 27 (19–38) | 28 (22–40) | 27 (20–38) n = 133 | .444 |
| Cirrhosis, n (%) | 16 (15) | 2 (6) | 18 (13) | .325 |
| Dominant stricture, n (%) | | | | .549 |
| No | 91 (83) | 28 (90) | 119 (85) | |
| Yes | 10 (9) | 2 (7) | 12 (9) | |
| Unknown | 9 (8) | 1 (3) | 10 (7) | |
| PSC diagnosed at anti-TNF start, n (%) | | | | .516 |
| No | 20 (18) | 3 (10) | 23 (16) | |
| Yes | 86 (78) | 27 (87) | 113 (80) | |
| Unknown | 4 (4) | 1 (3) | 5 (4) | |
| Portal hypertension, n (%) | | | | .412 |
| No | 90 (82) | 27 (87) | 117 (83) | |
| Yes | 4 (4) | 2 (7) | 6 (4) | |
| Unknown | 16 (15) | 2 (7) | 18 (13) | |
| Previous history of biliary dysplasia, n (%) | | | | .751 |
| No | 87 (79) | 25 (81) | 112 (79) | |
| Yes | 2 (2) | 0 (0) | 2 (1) | |
| Unknown | 21 (19) | 6 (19) | 27 (19) | |
| Type of IBD, n (%) | | | | .556 |
| UC | 68 (62) | 16 (52) | 84 (60) | |
| CD | 38 (35) | 14 (45) | 52 (37) | |
| IBD-U | 4 (4) | 1 (3) | 5 (4) | |
| History of colonic dysplasia, n (%) | | | | .945 |
| No | 87 (79) | 25 (81) | 112 (79) | |
| Yes | 13 (12) | 3 (10) | 16 (11) | |
| Unknown | 10 (9) | 3 (10) | 13 (9) | |
| Concomitant UDCA | | | | .893 |
| No | 55 (50) | 17 (55) | 72 (51) | |
| Yes | 47 (43) | 12 (39) | 59 (42) | |
| Unknown | 8 (7) | 2 (7) | 10 (7) | |
| Concomitant mesalamine | | | | .761 |
| No | 43 (39) | 13 (42) | 56 (40) | |
| Yes | 55 (50) | 16 (52) | 71 (50) | |
| Unknown | 12 (11) | 2 (7) | 14 (10) | |
| Concomitant cortisone | | | | .207 |
| No | 38 (35) | 16 (52) | 54 (38) | |
| Yes | 61 (56) | 12 (29) | 73 (52) | |
| Unknown | 11 (10) | 3 (10) | 14 (10) | |
| Concomitant immunosuppressants, n (%) | | | | .488 |
| No | 46 (42) | 16 (52) | 62 (44) | |
| Yes | 50 (46) | 13 (42) | 63 (45) | |
| Unknown | 14 (13) | 2 (7) | 16 (11) | |
| Duration of anti-TNF treatment, *d*, median (IQR) | 492 (239–1238) | 328 (262–1377) | 457 (251–1244) | .748 |

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; IQR, interquartile range; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

**Table 2.** Table of the Primary Reason for Stopping Anti-TNF Drug

| Primary reason for stopping anti-TNF drug | Infliximab, n = 147 | Adalimumab, n = 39 | Total, n = 186 |
|---|---|---|---|
| Adverse event, n (%) | 26 (18) | 8 (21) | 34 (18) |
| Primary nonresponder, n (%) | 27 (318) | 5 (13) | 32 (17) |
| Secondary loss of response, n (%) | 22 (15) | 4 (10) | 26 (14) |
| Remission, n (%) | 7 (5) | 2 (5) | 9 (5) |
| Lack of compliance, lost to follow-up evaluation, deceased, n (%) | 4 (3) | 0 (0) | 4 (2) |
| Other, n (%) | 3 (2) | 0 (0) | 3 (2) |

TNF, tumor necrosis factor.

was reported in 22 (23%) of 95 patients with available data, 67 (71%) were not in remission, and 6 (6%) patients had discontinued the drug. At 12 months, 41 (38%) of 109 patients with available data were responding to anti-TNF, 26 (24%) were not responding, and 42 (39%) had stopped anti-TNF. At 12 months, 20 (20%) of 102 patients with available data were in remission while 40 (39%) were judged not in remission and 42 (41%) had stopped anti-TNF.

### *Drug-Related Side Effects*

Additional patients were included in the analysis of the reasons for anti-TNF discontinuation (45 patients with available drug treatment data, but insufficient laboratory data). During the first year of treatment, 64 of 186 patients (34%) stopped anti-TNF, of whom 49 (26%) stopped owing to adverse events. Considering all available side-effect data (including beyond 1 year of treatment), 108 of 186 (58%) patients were recorded as having discontinued anti-TNF after a median of 539 days (interquartile range [IQR], 217–1101 d). The most common reasons were primary nonresponse (n = 32; 17%) and adverse events (n = 34; 18%) (Table 2). There were no significant differences between infliximab- and adalimumab-treated patients for the reasons for anti-TNF discontinuation ($P = .738$). In an additional 22 patients the drug was stopped primarily for another reason, but adverse events also were recorded, making a total of 58 adverse events reported in 56 patients (Table 3). Adverse events were similar between infliximab- and adalimumab-treated patients ($P = .894$).

### *Primary Sclerosing Cholangitis Outcomes*

PSC symptom prevalence was not significantly different between baseline and 12 months, except for abdominal pain, which was less frequent after 12 months compared with baseline (Supplementary Table 2). There was no difference between infliximab and adalimumab in PSC symptom frequency after drug exposure. Seven patients died, all more than 1 year (median, 2.4 y; IQR, 1.5–4.8 y) after initiation of anti-TNF. Among these, 6 received infliximab and 1 received adalimumab.

### *Liver Transplanted Patients*

Ten (8 infliximab-treated and 2 adalimumab-treated) patients underwent liver transplantation at a median of 2.3 years (IQR, 1.5–5.0 y; range, 0.5–6.5 y) before starting anti-TNF. These post-transplant patients were considered as a separate cohort from the data reported earlier. Demographic features of these patients were not different from the 141 nontransplanted patients (Supplementary Table 3).

IBD response data were available in 7 post-transplant patients, of whom 4 (57%) were judged to have responded at 3 months ($P = .780$ for the comparison with non–liver transplantation patients) and 5 (71%) responded at 12 months ($P = .690$ for the comparison with non–liver transplantation patients).

Data on 2 additional post-transplant patients were available for side-effect analysis. Seven of these 12 patients (58%) discontinued anti-TNF: 3 because of adverse events (1 each for allergic reaction, infection, and malignancy), 2 because of primary nonresponse, 1 because of remission, and 1 for unknown reasons.

### *Liver Biochemistry*

Liver biochemistry data were available for 90 patients, of whom 67 (74%) received infliximab and 23 (26%) received adalimumab. There was a small but significant decrease in the serum ALP level during the

**Table 3.** Table of All Adverse Events

| Adverse event | Infliximab, n = 147 | Adalimumab, n = 39 | Total, n = 186 |
|---|---|---|---|
| Allergy, n (%) | 11 (7) | 3 (8) | 14 (8) |
| Infection, n (%) | 10 (7) | 2 (5) | 12 (6) |
| Skin disease, n (%) | 7 (5) | 2 (5) | 9 (5) |
| Malignancy, n (%) | 3 (2) | 0 (0) | 3 (2) |
| SLE, n (%) | 1 (1) | 0 (0) | 1 (1) |
| Recurrent cholangitis, n (%) | 7 (5) | 1 (3) | 8 (4) |
| Unknown, n (%) | 8 (5) | 3 (38) | 11 (6) |

SLE, systemic lupus erythematosus.

**Table 4.** Change in Liver Biochemistry Between Baseline and Later Time Points

| | Infliximab | | Adalimumab | |
|---|---|---|---|---|
| | ALP × ULN, (IQR) | *P* value | ALP × ULN, (IQR) | *P* value |
| Baseline | 1.3 (0.8–2.4) | .306 (n = 66) | 1.1 (0.7–2.4) | .001 (n = 23) |
| 3 months[a] | 1.2 (0.7–2.1) | | 0.9 (0.6–1.6) | |
| Baseline | 1.4 (0.8–2.8) | .934 (n = 62) | 1.1 (0.7–2.5) | .004 (n = 18) |
| 6 months | 1.4 (0.7–2.6) | | 0.7 (0.6–1.9) | |
| Baseline | 1.4 (0.7–2.8) | .806 (n = 51) | 1.1 (0.7–2.1) | .011 (n = 14) |
| 12 months | 1.4 (0.7–2.6) | | 0.8 (0.6–1.5) | |

NOTE. Not all patients had values for serum alkaline phosphatase at every time point, and fewer patients still were being treated with the drug at each consecutive time point, hence the differing numbers of patients in each comparison.
ALP, alkaline phosphatase; IQR, interquartile range; ULN, upper limit of normal.
[a]Blood samples sent between 6 and 16 weeks are included here.

first 3 months of anti-TNF exposure (baseline: 1.19 ×ULN; IQR, 0.79–2.43; 3 months: 1.11 ×ULN; IQR, 0.68–1.89; $P$ =.025). However, when infliximab- and adalimumab-treated patients were considered separately, the change in ALP level was strikingly only seen with adalimumab (-15%; IQR, -29 to -4%) compared with infliximab (-4%; IQR, -25 to +19%; $P$ = .035). This difference also was apparent at 6 and 12 months (Table 4 and Figure 2). At baseline, there was no significant difference between infliximab- and adalimumab-treated patients in the proportion of patients with increased ALP level (infliximab: n = 40, 60%; adalimumab: n = 13, 57%; $P$ = .50) or in IBD activity (baseline C-reactive protein: infliximab: median, 2 ×ULN [n = 61]; adalimumab: median, 1.9 ×ULN [n = 20]; $P$ = .8); median fecal calprotectin (infliximab: median, 1306 μg/mg [n = 9]; adalimumab: median, 1000 μg/mg [n = 5]; $P$ = .36); and serum albumin (infliximab: median, 0.8 ×ULN [n = 62]; adalimumab: median 0.8 ×ULN [n = 20]; $P$ = .06). Of 81 patients with data available there was no difference in IBD response between infliximab (n = 27; 46%) and adalimumab (n = 13; 59%; $P$ = .207). The proportion of patients from European sites was similar for infliximab (n = 43; 64%) and adalimumab (n = 15; 65%; $P$ = .57).

Of the infliximab-treated patients, 27 had normal ALP level at baseline, and by 3 months 6 (22%) of these patients had an increased ALP level. Of the 40 infliximab-treated patients with increased ALP level at baseline, 6 (15%) had normalized their ALP level. Ten adalimumab-treated patients had a normal ALP level at baseline and all of them still had a normal ALP level after 3 months. Thirteen adalimumab patients had an increased ALP level at baseline, in whom 5 (38%) had normalized their ALP level after 3 months. The proportion of patients with a change in ALP level of more than 40% during the first 3 months of exposure to anti-TNF was analyzed to detect an effect of anti-TNF ALP level greater than the usual fluctuations expected in PSC.[9] Seven patients (11%) who had received infliximab and 4 (17%) who had received adalimumab experienced a decrease of ALP level greater than 40% ($P$ = .303). Eight patients (12%) who received infliximab experienced an increase in ALP level of greater than 40%, compared with none of the adalimumab-treated patients ($P$ = .081). The median maximum ALP level over the first 12 months in infliximab-treated patients was 1.31 ×ULN (IQR, 0.74–2.77), and in adalimumab-treated patients it was 0.89 ×ULN (IQR, 0.74–2.74; $P$ = .162).

Bilirubin level increased over the first 3 months of treatment (baseline median, 0.39 ×ULN [IQR, 0.24–0.66]; follow-up evaluation, 0.46 ×ULN [IQR, 0.29–0.65]; $P$ = .015; n = 64). This occurred in patients treated with infliximab (baseline, 0.33 ×ULN [IQR, 0.20–0.62]; follow-up evaluation, 0.46 ×ULN [IQR, 0.29–0.64]; $P$ = .003; n = 47), but not adalimumab (baseline, 0.58 ×ULN [IQR, 0.40–0.70]; follow-up evaluation, 0.5 ×ULN [IQR, 0.32–0.70]; $P$ = .65; n = 17). However, at baseline, the bilirubin level was significantly lower in patients who received infliximab (median, 0.33 ×ULN; IQR, 0.2–0.62) compared with adalimumab (median, 0.58 ×ULN; IQR, 0.39–0.70; $P$ = .025). Thus, after 3 months the bilirubin level was similar between infliximab patients (0.46; IQR, 0.29–0.64) and adalimumab patients (0.5 ×ULN; IQR, 0.32–0.7; $P$ = .78).

There was no difference between infliximab- and adalimumab-treated patients in the proportion with response, remission, or anti-TNF discontinuation at 3 either months or after 12 months. However, in the 100 patients with available data who were still on the anti-TNF, there was a nonsignificant trend toward a more frequent IBD response to adalimumab (15; 60%) compared with infliximab (35, 47%; $P$ = .356) at 3 months (6 patients had available data but had stopped anti-TNF, all 6 were infliximab-treated). There was no difference between infliximab and adalimumab in the proportion of patients treated with UDCA (47, 46%; and 12, 41%, respectively; $P$ = .679). ALP level was nonsignificantly higher in patients treated with UDCA at baseline (1.5 ×ULN) compared with patients without UDCA treatment (1.1 ×ULN; $P$ = .145), and was significantly higher at 3 months (1.4 ×ULN vs 0.9 ×ULN; $P$ = .005), and at 12 months (2.1 ×ULN vs 0.8 ×ULN; $P$ = .045) in patients treated with UDCA.

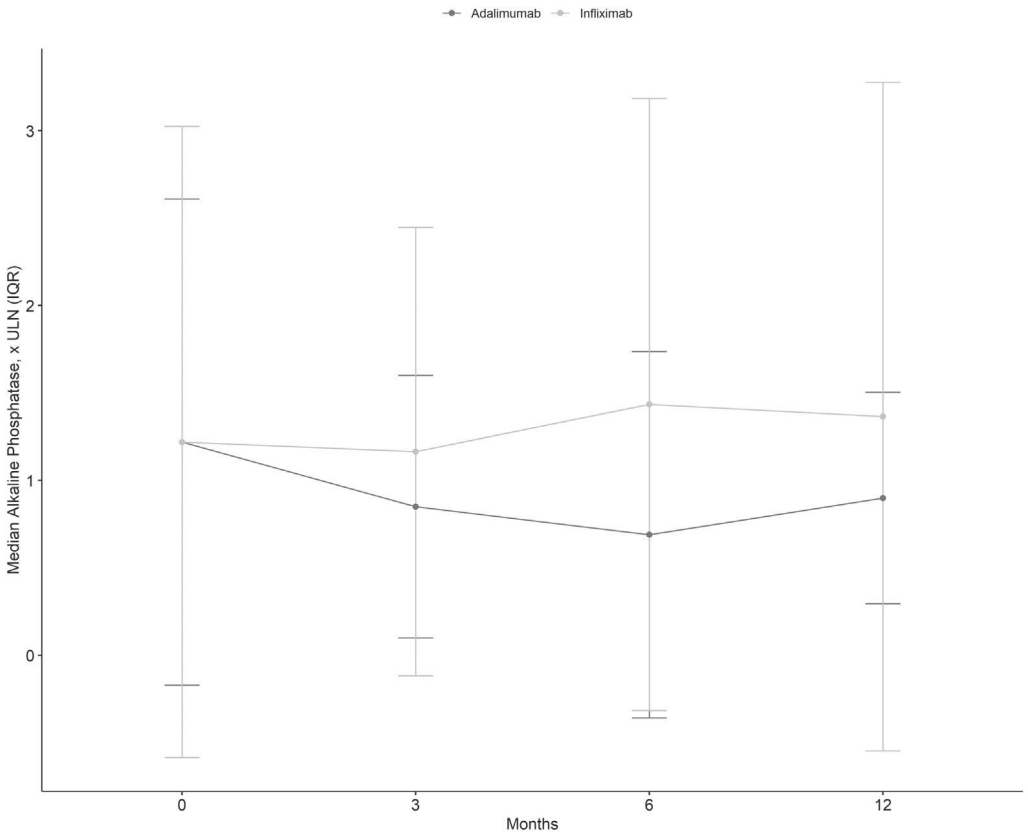


**Figure 2.** Variation in serum alkaline phosphatase (ALP) over time in infliximab- and adalimumab-treated patients. Only patients still taking the drug were included at each time point (baseline, n = 104; 3 months, n = 82; 6 months, n = 64; and 12 months, n = 54).

### *Regression Model of Factors Associated With Alkaline Phosphatase*

Multiple linear regression analysis was performed to identify factors associated with serum ALP level after 3 months of anti-TNF treatment. Predictor variables were as follows: site of treatment (North America or Europe), sex, age at IBD diagnosis (≤16, 17–40, >40 y), type of IBD (ulcerative colitis, Crohn's disease, and IBD unclassified), dominant stricture at baseline, increased baseline ALP level, which anti-TNF drug (infliximab or adalimumab), concomitant immunomodulator treatment or not, and IBD response to the anti-TNF or not. The outcome was ALP level at 3 months, which was natural log-transformed. The final model fit was significant ($F[3,61] = 18.86$; $P < .001$; $R^2 = 0.47$). The factors included in the final model were as follows: normal ALP level at baseline ($P < .01$), treatment with adalimumab ($P = .090$), and treatment at a European site ($P = .083$), all of which were predictive of a lower ALP level. Thus, adjusting for increased baseline ALP level and the site of treatment, patients on adalimumab had a 24% lower ALP level compared with patients on infliximab ($P = .090$). A similar analysis was performed for the 12-month time point. The final model fit was significant ($F[4,38] = 12.61$; $P < .001$; $R^2 = 0.55$). The factors included in this model were normal ALP level at baseline ($P < .01$), IBD response to the anti-TNF drug at 3 months ($P = .005$), treatment in Europe ($P = .059$), and treatment with adalimumab ($P = .078$), all of which were predictive of a lower ALP level. Thus, adjusting for an increased ALP level at baseline, site of treatment, and IBD response to the anti-TNF drug, patients treated with adalimumab had a 33% lower ALP level at 12 months compared with patients treated with infliximab.

### *Patients With Cirrhosis*

Eighteen patients had cirrhosis. Their median baseline ALP level was 1.9 ×ULN (IQR, 1.3–4.0; n = 17). There was no significant difference between baseline ALP level compared with 6 or 12 months. Similarly, the baseline serum bilirubin level in cirrhotic patients was 0.7 ×ULN (IQR, 0.6–1.3) and was not different compared with 6 or 12 months. Sixteen (89%) patients were treated with infliximab and 2 were treated with adalimumab, preventing analysis of a differential effect.

## Discussion

This study has collected a large cohort of PSC-IBD patients who have been treated with anti-TNF. These data showed clinical efficacy for IBD, albeit in a somewhat lower proportion of patients (48%) at 3 months compared with 62% to 96% early response rates to anti-TNF reported in real-world non–PSC-IBD cohorts.[10–13] PSC IBD differs from non-PSC IBD, as mentioned earlier.[1] It may be that attenuated response to anti-TNF is also a feature of this phenotype. The rate of drug

discontinuation owing to adverse events over the first treatment year was 23%, which is higher than the 8% to 13% rate previously reported in non-PSC patients.[14] However, the types of adverse events reported were similar to those seen in non-PSC IBD, specifically, only 1 case of recurrent cholangitis was reported as the reason for anti-TNF discontinuation. It may be that drug discontinuation was motivated by lack of response rather than adverse events.

There was no difference in the frequency of PSC-related symptoms in the year before compared with the year after anti-TNF initiation apart from a reduction in the frequency of abdominal pain, which may be related to the effect of anti-TNF on IBD. Specifically, there was no difference in the frequency of recurrent cholangitis. This infectious complication of PSC may lead to caution in starting anti-TNF agents, especially in patients with previous cholangitis. However, only 2 of the cases of cholangitis reported during anti-TNF treatment occurred in patients with cholangitis in the year before anti-TNF introduction. Thus, we did not detect evidence of an adverse effect of anti-TNF on PSC symptoms, indicating that PSC need not be a contraindication when starting anti-TNF.

The use of UDCA was associated with a higher ALP level at all time points, in contrast to studies showing that UDCA is associated with improvement in serum liver tests.[15] It is likely that a higher ALP level in UDCA-treated patients reflects a bias toward prescribing UDCA in patients with increased ALP. However, a Cochrane systematic review found no significant reduction in the relative risk outcomes such as death or liver transplant with UDCA in patients with PSC,[16] thus the clinical benefit of UDCA in PSC is not established.

Anti-TNF drug use was associated with lower serum ALP level. In the regression analyses, the only statistically significant factors contributing to the final model in predicting ALP level at follow-up evaluation were ALP level at baseline and IBD response at 3 months. However, we did observe a nonsignificant 33% reduction of ALP level in patients treated with adalimumab. It may be that, despite multinational collaboration, these data are underpowered to definitively show a difference between anti-TNF drugs. This interpretation is supported by the finding of similar effects of adalimumab but not infliximab in reducing ALP level in a separate, previously published cohort of PSC-IBD patients.[17] In contrast, 3 studies have examined the effect of vedolizumab on ALP level in PSC-IBD and not shown an effect on ALP level, indicating that the reduction in ALP level with anti-TNF may be a class effect.[17–19] A positive IBD response at 3 months was significantly predictive of a lower ALP level at 12 months, raising the question of whether the effect of adalimumab on ALP level could be dependent on the reduction of intestinal inflammation, rather than a direct effect on biliary function. This observation taken together with the lack of effect of vedolizumab on ALP level observed in other studies raises the question as to whether the transmission of the positive effects of anti-TNF from gut to liver may depend on $\alpha 4\beta 7$ integrin-driven lymphocyte homing. Further studies are needed to explore the mechanism by which anti-TNF agents may influence ALP level in PSC. Importantly, the use of immunomodulators, which themselves can affect liver function, was not different between infliximab- and adalimumab-treated patients, and was not predictive of serum ALP level. Treatment at a European site was predictive of lower ALP level, which may relate to nation-specific prescribing practices such as nonadherence to standard dosing schedules and drug access limitations.[20]

No evidence for a negative effect on ALP or bilirubin levels was detected in either cirrhotic patients or post–liver transplantation patients, indicating that there is at least no signal of worse outcomes with anti-TNF treatment in these patient groups.

The need to collaborate across 20 centers to generate this cohort emphasizes the challenge in studying this rare disease and the value of these data. Thus, despite limited numbers of patients, this represents a large study of anti-TNF in PSC IBD. Limitations of this study include its retrospective nature and the lack of a matched control group. Only a proportion of patients contributed to the analysis at each time point because data were not always available. Future studies also should use combinations of markers of response such as ALP, markers of fibrosis, cholangiography, and magnetic resonance imaging[8,21] to increase applicability.

In conclusion, this study has shown attenuated response to anti-TNF agents but no PSC-specific side effects in PSC IBD. The rate of anti-TNF discontinuation owing to adverse events may be higher and drug efficacy in treating IBD may be lower in PSC IBD compared with non-PSC IBD. No anti-TNF–associated adverse effects on liver function in patients with cirrhosis or post–liver transplantation patients was detected. A positive effect on serum ALP level was associated with adalimumab but not infliximab in PSC-IBD patients. These data, together with the study from Tse et al,[17] should motivate prospective studies of the potential advantages of adalimumab over infliximab in PSC IBD.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.02.014.

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**Supplementary Table 1.** Total Patients Included in the Main Analysis by Site

| Site | | No liver transplantation | Liver transplantation | Total |
|---|---|---|---|---|
| Europe | | | | |
| Karolinska University Hospital Stockholm | Sweden | 19 | 2 | 21 |
| Royal Free Hospital, London | United Kingdom | 11 | 1 | 12 |
| Skånes University Hospital Lund | Sweden | 11 | 0 | 11 |
| Oslo University Hospital, Ullevål | Norway | 7 | 0 | 7 |
| Amsterdam Medical Centre, Amsterdam | The Netherlands | 7 | 0 | 7 |
| Tel Aviv Medical Center, Tel Aviv | Israel | 6 | 0 | 6 |
| Joh Radcliffe Hospital, Oxford | United Kingdom | 6 | 0 | 6 |
| University Hospital Heidelberg, Heidelberg | Germany | 5 | 0 | 5 |
| Haraldsplass Deaconess Hospital, Bergen | Norway | 5 | 0 | 5 |
| Uppsala University Hospital, Uppsala | Sweden | 5 | 1 | 6 |
| University Medical Centre Hamburg-Eppendorf, Hamburg | Germany | 5 | 1 | 6 |
| University Hospitals Leuven, Leuven | Belgium | 5 | 0 | 5 |
| University Hospitals Padua, Padua | Italy | 2 | 0 | 2 |
| Sahlgrenska Academy and University Hospital, Gothenburg | Sweden | 1 | 0 | 1 |
| Hvidovre Hospital and Department of Hepatology Rigshospitalet, Copenhagen | Denmark | 1 | 2 | 3 |
| North America | | | | |
| University of Alberta, Edmonton | Canada | 31 | 3 | 34 |
| University of Miami Miller School of Medicine, Miami | United States | 7 | 0 | 7 |
| University of California Davis, Sacramento | United States | 7 | 0 | 7 |
| Total | | 141 | 10 | 151 |

**Supplementary Table 2.** Frequency of PSC Symptoms at Baseline (in the Year Before Starting Anti-TNF) and After Anti-TNF Treatment in Nontransplanted PSC Patients (n = 186)

| | Baseline, n/total (%) | After 12 months anti–TNF-$\alpha$, n/total (%) | *P* value |
|---|---|---|---|
| Portal hypertension (n = 158) | 11 (7) | 11 (7) | 1.00 |
| Dominant stricture (n = 168) | 14 (8) | 15 (9) | 1.00 |
| Biliary dysplasia (n = 140) | 3 (2) | 5 (4) | .50 |
| Pruritus (n = 165) | 22 (13) | 16 (10) | .37 |
| Recurrent cholangitis (n = 168) | 7 (4) | 8 (5) | 1.00 |
| Abdominal pain (n = 129) | 30 (23) | 16 (12) | .02 |
| Jaundice (n = 169) | 8 (5) | 13 (8) | .36 |

NOTE. Because of incomplete data, different numbers of patients contribute to the analysis of each symptom.
PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor.

**Supplementary Table 3.** Description of Post–Liver Transplant Patients Treated With Anti–TNF-$\alpha$

| Demographic factor | n = 10 |
|---|---|
| Male, n (%) | 7 (70) |
| Age at IBD diagnosis, *y*, median (IQR) | 19 (15–24) |
| Age at PSC diagnosis, *y*, median (IQR) | 25 (22–33) |
| Type of IBD, n (%) | |
| UC | 7 (70) |
| CD | 3 (30) |
| IBD unclassified | 0 (0) |
| Drug | |
| Infliximab | 8 (80) |
| Adalimumab | 2 (20) |
| Duration of anti-TNF treatment, *d*, median (IQR) | 471 (270–922) |
| ALP at baseline, ×ULN, (IQR) | 2.8 (1.6–3.7) |
| ALP during the first 3 months, ×ULN, (IQR) | 3.0 (2.0–4.5) |
| Bilirubin at baseline, ×ULN, (IQR) | 0.9 (0.7–1.7) |
| Bilirubin during at 3 months, ×ULN, (IQR) | 1.2 (0.5–1.6) |
| IBD response at 3 months, number/total (%) | 4/7 (57) |
| IBD response at 12 months, number/total (%) | 5/7 (71) |

ALP, alkaline phosphatase; CD, Crohn's disease; IBD, inflammatory bowel disease; IQR; interquartile range; PSC, primary sclerosing cholangitis; TNF, tumor necrosis factor; UC, ulcerative colitis; ULN; upper limit of normal.