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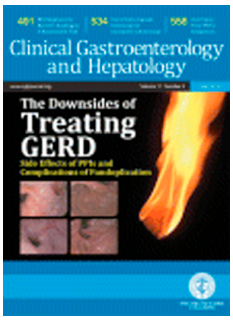

Effects of Tumor Necrosis Factor Antagonists in Patients With Primary Sclerosing Cholangitis

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PII: S1542-3565(20)30182-8
DOI: https://doi.org/10.1016/j.cgh.2020.02.014
Reference: YJCGH 57004

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 3 February 2020

Please cite this article as: Hedin CRH, Sado G, Ndegwa N, Lytvyak E, Mason A, Montano-Loza A, Gerussi A, Saffioti F, Thorburn D, Nilsson E, Larsson G, Moum BA, van Munster KN, Ponsioen CY, Levy C, Nogueira NF, Bowlus CL, Gotlieb N, Shibolet O, Lynch KD, Chapman RW, Rupp C, Vesterhus M, Jørgensen KK, Rorsman F, Schramm C, Sabino J, Vermeire S, Zago A, Cazzagon N, Marschal HU, Ytting H, Ben Belkacem K, Chazouilleres O, Almer S, Bergquist. A, International PSC study group (IPSCSG), Effects of Tumor Necrosis Factor Antagonists in Patients With Primary Sclerosing Cholangitis, *Clinical Gastroenterology and Hepatology* (2020), doi: https://doi.org/10.1016/j.cgh.2020.02.014.

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Running title: Anti-TNF in PSC

Word count including references: 4000 including the figure and table legends, and references.

Acknowledgement: Dr Å. Krantz,

This work was supported by the Stockholm County Council, Swedish Cancer Society and CRHH was supported by a Bengt Ihre Fellowship.

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Gastrointestinal Diseases

Patient Area Gastroenterology, Dermatovenerology and Rheumatology

Inflammation and Infection Theme

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Conflict of interest statement for all authors

C.R.H. Hedin: Speaker fees from Takeda, Ferring, Abbvie and Janssen, consultancy fees from Pfizer.

G. Sado: No personal or financial conflicts to disclose

N. Ndegwa: No personal or financial conflicts to disclose

E. Lytvyak: No personal or financial conflicts to disclose

A. Mason: No personal or financial conflicts to disclose

A. Montano-Loza: No personal or financial conflicts to disclose

A. Gerussi: No personal or financial conflicts to disclose

F. Saffioti: No personal or financial conflicts to disclose

D. Thorburn: No personal or financial conflicts to disclose

E. Nilsson: No personal or financial conflicts to disclose

G. Larsson: No personal or financial conflicts to disclose

B. A. Moum: No personal or financial conflicts to disclose

K.N. van Munster: No personal or financial conflicts to disclose

C.Y. Ponsioen: Grant support from Takeda, speaker's fees from Takeda and Tillotts, and consultancy fees from Takeda and Pliant.

C. Levy: No personal or financial conflicts to disclose

N.F. Nogueira: No personal or financial conflicts to disclose

C.L. Bowlus: Advisory boards for BiomX, Intercept and GlaxoSmithKline and has received research grants from BiomX, Gilead, Intercept, CymaBay, Takeda, Bristol-Myers Squibb, GlaxoSmithKline, Tobira, Merck, TaiwanJ, Eli Lilly, Novartis, and Target Pharmasolutions.

N. Gotlieb: No personal or financial conflicts to disclose

O. Shibolet: No personal or financial conflicts to disclose

K. D. Lynch: Conference travel expenses from Norgine, Takeda, Dr Falk, Intercept Pharmaceuticals and MSD; speaker fees es from Dr Falk; consulting fees from Intercept Pharmaceuticals; and conference registration support from Ferring Pharmaceuticals.

R. W. Chapman: No personal or financial conflicts to disclose

C. Rupp: No personal or financial conflicts to disclose

M. Vesterhus: Advisory Board member for Intercept.

K.K. Jørgensen: No personal or financial conflicts to disclose

F. Rorsman: No personal or financial conflicts to disclose

C. Schramm: No personal or financial conflicts to disclose

J. Sabino: Speaker fees from Abbvie.

S. Vermeire: Grant support from AbbVie, Janssen, MSD, Pfizer and Takeda; speaker fees from AbbVie, Dr. Falk Pharma, Ferring, Hospira, MSD, Pfizer, Takeda and Tillots; Consultant for AbbVie, Arena, Amgen, Celgene, Eli Lilly, Ferring, Galapagos, Genentech/Roche, Gilead, Hospira, Janssen, MSD, Mundipharma, Pfizer, ProDigest, Progenity, Second Genome, Shire and Takeda.

A. Zago: No personal or financial conflicts to disclose

N. Cazzagon: No personal or financial conflicts to disclose

H.U. Marschal: No personal or financial conflicts to disclose

H. Ytting: No personal or financial conflicts to disclose

K. Ben Belkacem: No personal or financial conflicts to disclose

O. Chazouilleres: No personal or financial conflicts to disclose

S. Almer: AbbVie – research grants, Janssen - advisory board, consultancy, lecture fee Takeda - advisory board, consultancy, Tillotts – consultancy.

A. Bergquist: No personal or financial conflicts to disclose

Involvement of each author in the manuscript:

C.R.H. Hedin: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; G. Sado: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for

important intellectual content; statistical analysis, N. Ndegwa: Analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. E. Lytvyak: Acquisition of data; critical revision of the manuscript for important intellectual content. A. Mason: Acquisition of data; critical revision of the manuscript for important intellectual content. Montano-Loza: Acquisition of data; critical revision of the manuscript for important intellectual content. A. Gerussi: Acquisition of data; critical revision of the manuscript for important intellectual content. F. Saffioti: Acquisition of data; critical revision of the manuscript for important intellectual content. D. Thorburn: Acquisition of data; critical revision of the manuscript for important intellectual content. E. Nilsson: Acquisition of data; critical revision of the manuscript for important intellectual content. G. Larsson: Acquisition of data; critical revision of the manuscript for important intellectual content. B. A. Moum: Acquisition of data; critical revision of the manuscript for important intellectual content. K.N. van Munster: Acquisition of data; critical revision of the manuscript for important intellectual content. C.Y. Ponsioen: Acquisition of data; critical revision of the manuscript for important intellectual content. C. Levy: Acquisition of data; critical revision of the manuscript for important intellectual content. N.F. Nogueira: Acquisition of data; critical revision of the manuscript for important intellectual content. C.L. Bowlus: Acquisition of data; critical revision of the manuscript for important intellectual content. N. Gotlieb: Acquisition of data; critical revision of the manuscript for important intellectual content. O. Shibolet: Acquisition of data; critical revision of the manuscript for important intellectual content. K. D. Lynch: Acquisition of data; critical revision of the manuscript for important intellectual content. R. W. Chapman: Acquisition of data; critical revision of the manuscript for important intellectual content. C. Rupp: Acquisition of data; critical revision of the manuscript for important intellectual

content. M. Vesterhus: Acquisition of data; critical revision of the manuscript for important intellectual content. K.K. Jørgensen: Acquisition of data; critical revision of the manuscript for important intellectual content. F. Rorsman: Acquisition of data; critical revision of the manuscript for important intellectual content. C. Schramm: Acquisition of data; critical revision of the manuscript for important intellectual content. J. Sabino: Acquisition of data; critical revision of the manuscript for important intellectual content. S. Vermeire: Acquisition of data; critical revision of the manuscript for important intellectual content. A. Zago: Acquisition of data; critical revision of the manuscript for important intellectual content. N. Cazzagon: Acquisition of data; critical revision of the manuscript for important intellectual content. H.U. Marschal: Acquisition of data; critical revision of the manuscript for important intellectual content. H. Ytting: Acquisition of data; critical revision of the manuscript for important intellectual content. K. Ben Belkacem: Acquisition of data; critical revision of the manuscript for important intellectual content. O. Chazouilleres: Acquisition of data; critical revision of the manuscript for important intellectual content. S. Almer: Study concept and design; critical revision of the manuscript for important intellectual content; A. Bergquist: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis.

Abstract:

Background & Aims: Few patients with primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD) 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.

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 serum level of alkaline phosphatase (ALP). IBD response was defined as either endoscopic response or, if no endoscopic data available, clinical response, determined by the treating clinician or measurements of fecal. Remission was defined more stringently as endoscopic mucosal healing. We used linear regression analysis to identify factors significantly associated 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 non-response 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 further investigate the association between use of adalimumab and reduced serum levels of ALP.

KEY WORDS: hepatic; anti-inflammatory; intestine; liver transplantation

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 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.

Abbreviations

ALP - Alkaline phosphatase

CD - Crohn´s disease

CRP – C-reactive protein

IBD - Inflammatory bowel disease

IQR - Inter-quartile range

UDCA – Ursodeoxycholic acid

PSC - Primary sclerosing cholangitis

TNF – Tumor necrosis factor-α

UC - Ulcerative colitis

ULN - Upper limit of normal

Introduction

Anti-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 closely associated: the prevalence of IBD in PSC is 60-80%. 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 are often 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 aTNF 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 positively affect PSC. 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 UC.[6] Knowledge of immunological 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]

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 carried out via the International PSC Study group (IPSCSG, 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 bloods (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, 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.

Laboratory parameters collected before and after treatment (0, 3, 6, 12 months) were: blood counts, serum biochemistry (including liver biochemistry) and fecal calprotectin. Patients were only included if they had follow-up bloods at least in one 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 fell between these time periods were omitted. Where there was more than one 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 (xULN). IBD response was defined as either endoscopic response or, where endoscopic data were not available, clinical response as determined by the treating clinician, or a drop in fecal calprotectin of ≥30% from baseline or absolute value <250 μg/g. Remission was defined more stringently as endoscopic mucosal healing or, where endoscopic data were unavailable, as clinical remission according to the physicians assessment.

Outcomes

Alkaline phosphatase (ALP) is a recognized surrogate marker for PSC treatment response, [9] and this was used as a marker 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 Wilcoxon signed rank or Kruskall-Wallis tests. Differences between groups were analyzed using Mann-Whitney U

tests. Categorical values were compared using chi-squared tests and correlations were assessed with Spearman's rank correlation coefficient. Longitudinal comparison of binary variables was carried out using McNemar's test. Multiple linear regression analyses were carried out 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.

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 (e.g. no baseline ALP 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 who started anti-TNF whilst on UDCA all but 4 remained on UDCA for the whole of the first year. Of those not taking UDCA at baseline only 8 started UDCA during the first year.

IBD 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 non-responders and 6 (6%) had discontinued anti-TNF. Remission at 3 months 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 whilst 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 which 49 (26%) stopped due 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 (IQR 217-1101 days). The most common reasons were primary non-response (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 were also 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).

PSC 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 >1

year (median 2.4, IQR 1.5-4.8 years) after initiation of anti-TNF. Among these, 6 received infliximab and one adalimumab.

Liver transplanted patients

Ten (8 infliximab- and 2 adalimumab-treated) patients underwent liver transplantation at a median of 2.3 years (IQR 1.5-5.0, range 0.5-6.5 years) before starting anti-TNF. These post-transplant patients were considered as a separate cohort from the data reported above. Demographic features of these patients were not different from the 141 non-transplanted 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%) 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 (allergic reaction, infection and malignancy respectively), 2 because of primary non-response, 1 because of remission and 1 for unknown reasons.

Liver biochemistry

Liver biochemistry data were available for 90 patients, of which 67 (74%) received infliximab and 23 (26%) adalimumab. There was a small, but significant fall in the serum ALP during the first three months of anti-TNF exposure, (baseline 1.19 xULN (IQR 0.79-2.43), 3 months 1.11 xULN (IQR 0.68-1.89), *P*=.025). However, when infliximab- and adalimumab-treated patients were considered separately, the change in ALP was strikingly only seen with adalimumab (-15% (inter-quartile range (IQR) -29 to -4%))

compared with infliximab (-4%, (IQR -25 to +19%), *P*=.035). This difference was also 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 raised ALP (infliximab (n=40, 60%); adalimumab (n=13, 57%, *P*=.50) or in IBD activity (baseline CRP (infliximab median 2 xULN (n=61), adalimumab median 1.9 xULN (n=20), *P*=.8); median fecal calprotectin (infliximab median 1306 μg/mg (n=9), adalimumab median 1000 μg/mg (n=5), *P*=.36); serum albumin (infliximab median 0.8 xULN (n=62), adalimumab 0.8 xULN (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 at baseline and by 3 months 6 (22%) of these had raised ALP. Of the 40 infliximab-treated patients with raised ALP at baseline, 6 (15%) had normalized their ALP. Ten adalimumab-treated patients had normal ALP at baseline and all of them still had normal ALP after 3 months. Thirteen adalimumab patients had raised ALP at baseline in which 5 (38%) the ALP normalized after 3 months. The proportion of patients with a change in ALP >40% during first 3 months of exposure to anti-TNF was analyzed in order to detect an effect of anti-TNF ALP above the usual fluctuations expected in PSC.[9] Seven patients (11%) who had received infliximab and 4 (17%) who had received adalimumab experienced a fall of ALP >40%, (*P*=.303). Eight patients (12%) who received infliximab experienced an increase in ALP of >40%, compared with none of the adalimumab-treated patients, (*P*=.081). The median maximum ALP over the first 12 months in infliximab-treated patients was 1.31 xULN (IQR 0.74-2.77) and adalimumab treated patients it was 0.89 xULN (IQR 0.74-2.74, *P*=.162).

Bilirubin rose over the first 3 months of treatment, (baseline median 0.39 xULN (IQR 0.24-0.66), follow-up 0.46 xULN (IQR 0.29-0.65), *P*=.015, n=64). This occurred in patients treated with infliximab (baseline 0.33 xULN (IQR 0.20-0.62), follow-up 0.46 xULN (IQR 0.29-0.64), *P*=.003, n=47) but not adalimumab (baseline 0.58 xULN (IQR 0.40-0.70), follow-up 0.5 xULN (IQR 0.32-0.70), *P*=.65, n=17). However, at baseline bilirubin was significantly lower in patients who received infliximab (median 0.33 xULN (IQR 0.2-0.62)) compared with adalimumab (median 0.58 xULN (IQR 0.39-0.70), *P*=.025). Thus, after 3 months bilirubin was similar between infliximab patients (0.46 (IQR 0.29-0.64)) and adalimumab patients (0.5 xULN, (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 either at 3 months or after 12 months. However, in the 100 patients with available data who were still on the anti-TNF, there was a non-significant trend towards 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, all6 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 was non-significantly higher in patients treated with UDCA at baseline (1.5x ULN) compared with those without UDCA (1.1x ULN, *P*=.145) and was significantly higher at 3 months (1.4 xULN vs 0.9 x ULN, *P*=.005) and at 12 months (2.1x ULN vs 0.8 xULN, *P*=.045) in patients treated with UDCA.

Regression model of factors associated with alkaline phosphatase

Multiple linear regression analysis was carried out in order to identify factors associated with serum ALP after 3 months of anti-TNF treatment. Predictor variables were: site of

treatment (North America or Europe), sex, age at IBD diagnosis (≤16, 17-40, >40 years), type of IBD (UC, CD, IBD-unclassified), dominant stricture at baseline, raised baseline ALP, 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 at 3 months which was natural log-transformed. The final model fit was significant ($F(3,61)=18.86$, $p<0.001$) $R^2= 0.47$. The factors included in the final model were: normal ALP at baseline ($p<0.01$), treatment with adalimumab (P=.090) and treatment at a European site (P=.083) all of which were predictive of a lower ALP. Thus, adjusting for raised baseline ALP and the site of treatment, those on adalimumab had 24% lower ALP compared with those on infliximab, (P=.090). A similar analysis was performed for the 12 month time point. The final model fit was significant ($F(4,38)=12.61$, $p<0.001$), $R^2=$ 0.55. The factors included in this model were normal ALP at baseline (P<0.01), IBD-response to the anti-TNF drug at 3 months (P=.005), treatment in Europe (P=.059) and treatment with adalimumab (P=.078), which were all predictive of lower ALP. Thus, adjusting for raised ALP at baseline, site of treatment and IBD response to the anti-TNF drug, patients treated with adalimumab had 33% lower ALP at 12 months compared with those treated with infliximab.

Patients with cirrhosis

Eighteen patients had cirrhosis. Their median baseline ALP was 1.9 x ULN (IQR 1.3-4.0) (n=17). There was no significant difference between baseline ALP compared with 6 or 12 months. Similarly, baseline serum bilirubin in cirrhotic patients was 0.7 x 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 with adalimumab, preventing analysis of a differential effect.

Discussion

This study has collected one of the largest cohorts of PSC-IBD patients who have been treated with anti-TNF. These data demonstrated clinical efficacy for IBD albeit in a somewhat lower proportion of patients (48%) at 3 months compared with 62-96% 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 above.[1] It may be that attenuated response to anti-TNF is also a feature of this phenotype. The rate of drug discontinuation due to adverse events over the first treatment year was 23% which is higher than the 8-13% 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 one 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 prior to 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 contra-indication when starting anti-TNF.

The use of UDCA was associated with higher ALP at all time points, in contrast to studies demonstrating that UDCA is associated with improvement in serum liver tests.[15] It is

likely that higher ALP in UDCA-treated patients reflects a bias toward prescribing of UDCA in patients with raised ALP. However, a Cochrane systematic review found no significant reduction in the relative risk outcomes such as death or liver transplant with UDCA in PSC,[16] thus the clinical benefit of UDCA in PSC is not established.

Anti-TNF drug use was associated with lower serum ALP. In the regression analyses the only statistically significant factors contributing to the final model in predicting ALP at follow-up were ALP at baseline and IBD-response at 3 months. However, we did observe a non-significant 33% reduction of ALP in patients treated with adalimumab. It may be that, despite multinational collaboration these data are underpowered to definitively demonstrate a difference between anti-TNF drugs. This interpretation is supported by the finding of similar effect of adalimumab but not infliximab in reducing ALP in a separate, previously published cohort of PSC-IBD patients.[17] In contrast, 3 studies have examined the effect of vedolizumab on ALP in PSC-IBD and not demonstrated an effect on ALP, indicating that the reduction in ALP with anti-TNF may be a class effect.[17-19] A positive IBD response at 3 months was significantly predictive of lower ALP at 12 months, raising the question of whether the effect of adalimumab on ALP could be dependent on 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 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 α4β7 integrin driven lymphocyte homing. Further studies are needed explore the mechanism by which anti-TNF agents may influence ALP in PSC. Importantly, the use of immunomodulators, which can themselves affect liver function, was not different between infliximab- and adalimumab-treated patients and was not predictive of serum ALP. Treatment at a European site was predictive of lower ALP which may relate to

nation-specific prescribing practices such as non-adherence to standard dosing schedules and drug access limitations.[20]

No evidence for a negative effect on ALP or bilirubin 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 one of the largest studies of anti-TNF in PSC-IBD to date. 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 as data were not always available. Future studies should also employ 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 demonstrated attenuated response to anti-TNF agents but no PSC-specific side-effects in PSC-IBD. The rate of anti-TNF discontinuation due to adverse events may be higher and drug efficacy in treating IBD lower in PSC-IBD compared with non-PSC IBD. No anti-TNF-associated adverse effect on liver function in patients with cirrhosis or post-liver transplantation patients was detected. A positive effect on serum ALP 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.

Figure legends

Figure 1. Flow diagram of patient exclusion: Patients were excluded if data on type if anti-TNF or laboratory data were insufficient. Patients with liver transplantation prior to initiation of anti-TNF were considered separately.

Figure 2. Variation in serum 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). ULN= upper limit of normal, IQR= interquartile range.

Tables

Table 1. Demographic factors at baseline of 141 non- transplanted 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)	0.550
Age at IBD diagnosis years, median (IQR)		19 (15-30)	21 (14-28)	20 (15-30) n=137	0.983
Age at PSC diagnosis years, median (IQR)		27 (19-38)	28 (22-40)	27 (20-38) n=133	0.444
Cirrhosis, n (%)		16 (15)	2 (6)	18 (13)	0.325
Dominant stricture, n (%)	**No**	91 (83)	28 (90)	119 (85)	0.549
	Yes	10 (9)	2 (7)	12 (9)	
	Unknown	9 (8)	1 (3)	10 (7)	
PSC diagnosed at aTNF start, n (%)	**No**	20 (18)	3 (10)	23 (16)	0.516
	Yes	86 (78)	27 (87)	113 (80)	
	Unknown	4 (4)	1 (3)	5 (4)	
Portal hypertension, n (%)*	**No**	90 (82)	27 (87)	117 (83)	0.412
	Yes	4 (4)	2 (7)	6 (4)	
	Unknown	16 (15)	2 (7)	18 (13)	
Previous history of biliary dysplasia, n (%)	**No**	87 (79)	25 (81)	112 (79)	0.751
	Yes	2 (2)	0 (0)	2 (1)	
	Unknown	21 (19)	6 (19)	27 (19)	

Type of IBD, n (%)	**UC**	68 (62)	16 (52)	84 (60)	0.556
	CD	38 (35)	14 (45)	52 (37)	
	IBD-U	4 (4)	1 (3)	5 (4)	
History of colonic dysplasia, n (%)	**No**	87 (79)	25 (81)	112 (79)	0.945
	Yes	13 (12)	3 (10)	16 (11)	
	Unknown	10 (9)	3 (10)	13 (9)	
Concomitant UDCA	**No**	55 (50)	17 (55)	72 (51)	0.893
	Yes	47 (43)	12 (39)	59 (42)	
	Unknown	8 (7)	2 (7)	10 (7)	
Concomitant 5ASA	**No**	43 (39)	13 (42)	56 (40)	0.761
	Yes	55 (50)	16 (52)	71 (50)	
	Unknown	12 (11)	2 (7)	14 (10)	
Concomitant cortisone	**No**	38 (35)	16 (52)	54 (38)	0.207
	Yes	61 (56)	12 (29)	73 (52)	
	Unknown	11 (10)	3 (10)	14 (10)	
Concomitant immuno-suppressants, n (%)	**No**	46 (42)	16 (52)	62 (44)	0.488
	Yes	50 (46)	13 (42)	63 (45)	
	Unknown	14 (13)	2 (7)	16 (11)	
Duration of anti-TNF treatment, days median (IQR)		492 (239-1238)	328 (262-1377)	457 (251-1244)	0.748

IBD: Inflammatory bowel disease, PSC: Primary sclerosing cholangitis, CD: Crohn's disease, UC: Ulcerative colitis, IBD-U: IBD-unclassified, UDCA: ursodeoxycholic acid, 5ASA: 5-aminosalicylic acid, IQR; Inter-quartile range,

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**
	Number of patients (%)		
Adverse event	26 (18)	8 (21)	34 (18)
Primary non-responder	27 (318)	5 (13)	32 (17)
Secondary loss of response	22 (15)	4 (10)	26 (14)
Remission	7 (5)	2 (5)	9 (5)
Lack of compliance, lost to follow-up, deceased	4 (3)	0 (0)	4 (2)
Other	3 (2)	0 (0)	3 (2)

Table 3 Table of all adverse events.

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

Table 4. Change in liver biochemistry between baseline and later time points. Not all patients had values for serum alkaline phosphatase at every time point and fewer patients were still being treated with the drug at each consecutive time point, hence differing numbers of patients in each comparison.

	Infliximab		**Adalimumab**	
	ALP x ULN, (IQR)	***P*-value**	**ALP x ULN, (IQR)**	***P*-value**
Baseline	1.3 (0.8-2.4)	0.306 (n=66)	1.1 (0.7-2.4)	0.001 (n=23)
3 months*	1.2 (0.7-2.1)		0.9 (0.6-1.6)	
Baseline	1.4 (0.8-2.8)	0.934 (n=62)	1.1 (0.7-2.5)	0.004 (n=18)
6 months	1.4 (0.7-2.6)		0.7 (0.6-1.9)	
Baseline	1.4 (0.7-2.8)	0.806 (n=51)	1.1 (0.7-2.1)	0.011 (n=14)
12 months	1.4 (0.7-2.6)		0.8 (0.6-1.5)	

ALP: Alkaline phosphatase, ULN: Upper Limit of Normal, IQR: Inter-quartile range

* Blood samples sent between 6 and 16 weeks included here

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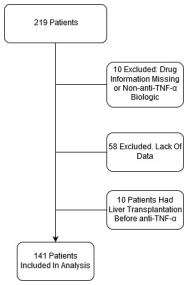

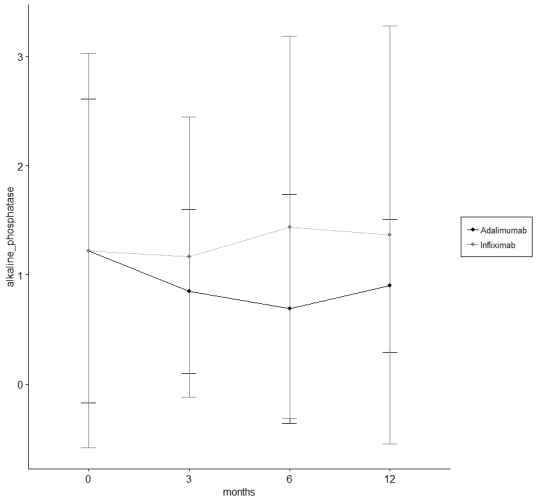

Supplementary tables

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	UK	11	1	12
Skånes University Hospital Lund	Sweden	11	0	11
Oslo University Hospital, Ullevål	Norway	7	0	7
Amsterdam Medical Centre, Amsterdam	Netherlands	7	0	7
Tel Aviv Medical Center, Tel Aviv	Israel	6	0	6
Joh Radcliffe Hospital, Oxford	UK	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	USA	7	0	7
University of California Davis, Sacramento,	USA	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 non-transplanted PSC patients, (n=186).Due to incomplete data different numbers of patients contribute to the analysis of each symptom

	Baseline n/total (%)	**After 12 months anti-TNF-α 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)	0.50
Pruritus (n=165)	22 (13)	16 (10)	0.37
Recurrent cholangitis (n=168)	7 (4)	8 (5)	1.00
Abdominal pain (n=129)	30 (23)	16 (12)	0.02
Jaundice (n=169)	8 (5)	13 (8)	0.36

Supplementary Table 3. Description of post-liver transplant patients treated with anti-TNF-α

Demographic factor		n=10
Male, n (%)		7 (70)
Age at IBD diagnosis years, median (IQR)		19 (15-24)
Age at PSC diagnosis years, 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, days median (IQR)		471 (270-922)
ALP at baseline, xULN, (IQR)		2.8 (1.6-3.7)
ALP during the first 3 months, xULN, (IQR)		3.0 (2.0-4.5)
Bilirubin at baseline, xULN, (IQR)		0.9 (0.7-1.7)
Bilirubin during at 3 months, xULN, (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)

ULN; Upper Limit of Normal, IQR; Inter-quartile range