Journal of Crohn's and Colitis, 2017, 1146–1151
doi:10.1093/ecco-jcc/jjx057
Advance Access publication May 6, 2017
Short Report

Short Report

Safety of Anti-TNF Treatment in Liver Transplant Recipients: A Systematic Review and Meta-analysis

M. J. Westerouen van Meeteren,[a] B. Hayee,[b] A. Inderson,[a] A. E. van der Meulen,[a] R. Altwegg,[c] B. van Hoek,[a] G. P. Pageaux,[c] T. Stijnen,[d] D. Stein,[e] P. W. J. Maljaars[a]

[a]Leiden University Medical Centre, Department of Gastroenterology-Hepatology, Leiden, The Netherlands [b]King's College Hospital, Department of Gastroenterology, London, UK [c]University Hospital of St Eloi, Department of Hepatology and Gastroenterology, Montpellier, France [d]Leiden University Medical Centre, Department of Medical Statistics, Leiden, The Netherlands [e]Medical College of Wisconsin, Department of Gastroenterology and Hepatology, Milwaukee, WI, USA

Corresponding author: Dr P. W. J. [Jeroen] Maljaars, MD, PhD, Department of Gastroenterology-Hepatology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. Tel.: +3171526911; Fax: +31715248115; Email: P.W.J.Maljaars@LUMC.nl

Abstract

Background and Aim: Little is known about the risk of serious infection when combining anti-tumour necrosis factor [TNF] therapy for refractory inflammatory bowel disease [IBD] with immunosuppression after liver transplantation [LT]. Our aim was to investigate the infection risk in this patient group by systematic review and meta-analysis of the available data.

Methods: A search was conducted for full papers and conference proceedings through September 2015, regarding liver transplant recipients and anti-TNF therapy. All studies were appraised using the adapted Newcastle-Ottawa Scale [NOS]. Two reviewers independently extracted patient data [age, duration of follow-up, number of all infections, number of serious infections, time since transplant]. As an additional control population, primary sclerosing cholangitis [PSC]-IBD patients from the Leiden University Medical Center [LUMC] LT cohort were used. Poisson regression was used to compare serious infections (according to International Conference on Harmonisation [ICH] definition) per patien-year follow-up between the anti-TNF and control groups.

Results: In all 465 articles and abstracts were identified, of which eight were included. These contained 53 post-LT patients on anti-TNF therapy and 23 post-LT patients not exposed to anti-TNF therapy. From the LUMC LT-cohort, 41 PSC patients with PSC-IBD not exposed to anti-TNF therapy were included as control population. The infection rate for TNF-exposed patients was 0.168 serious infections per patient year, compared with 0.149 in the control patients (rate ratio 1.12 [95% confidence interval: 0.233–5.404, $P = 0.886$]. When correcting for time since transplant, the infection rate was 0.194 in the TNF-exposed vs 0.115 in the non-exposed [$p = 0.219$].

Conclusions: No significant increase in the rate of serious infection was observed in LT recipients with PSC-IBD during exposure to anti-TNF therapy.

Key Words: liver transplantation, inflammatory bowel disease, primary sclerosing cholangitis, safety, biological therapy

1. Introduction

Primary sclerosing cholangitis [PSC] is an inflammatory and fibrosing liver disease involving the intra- and extrahepatic biliary tract. As no pharmaceutical or other disease-modifying therapeutic agent is available, a substantial portion of the patients eventually progress to end-stage liver disease or develop cholangiocarcinoma, requiring liver transplantation [LT].[1]

Nearly 70% of PSC patients have concurrent inflammatory bowel disease [IBD][3] and, after liver transplantation, IBD activity increases in one-third of patients.[4] This group poses a difficulty for the treating physician when mucosal healing is not achieved with conventional anti-inflammatory drugs. Anti-TNF therapy has been shown to be effective in both inducing and maintaining remission in IBD patients with refractory disease,[5] but was associated with an increase in the incidence of [serious] infections in some studies.[6] In liver transplant recipients, infections are important cause of mortality after LT.[7,8] Data on the risk of serious infection when combining anti-TNF therapy for IBD treatment with immunosuppression for prevention of rejection are scarce. To assess the safety of anti-TNF therapy in these patients, we performed a systematic review and meta-analysis in order to calculate and compare the serious infection rate in liver transplant recipients with and without anti-TNF exposure.

2. Methods

This study was conducted in accordance with the PRISMA statement.[9]

2.1. Search strategy

A systematic literature search was conducted of the following databases: PubMed, Embase, COCHRANE and Web of Science, for full papers, letters and abstracts. The literature search was performed by two authors [MWvM, PWJM] and a library information specialist. All entries were searched up to January 2017. The complete search strategy is available in Supplementary Data, available at *ECCO-JCC* online.

2.2. Study selection

Two authors independently reviewed the titles and abstracts of the identified papers, letters, and abstracts, and selected them for detailed assessment. These full articles, letters and abstracts were reviewed to select studies eligible for our final analysis. Studies were considered eligible if they met the following criteria: [I] the studies had to report on the incidence of serious infections in post-transplantation patients under treatment with any anti-TNF therapy for IBD; [II] the intervention of interest was concurrent anti-TNF-therapy and immunosuppression against transplant rejection, but concurrent use of other IBD medication was permitted; [III] studies could be of prospective and retrospective nature; [IV] studies without a control group were included in our selection, to maximize data quantity; [V] studies could not contain duplicate data already published; [VI] studies were written in English; and [VII] studies contained all data needed for analysis or data were provided by an author [Combes, Modiri, Pavlidis].As an additional source of control patient data, patients from the Leiden University Medical Center [LUMC] liver transplantation cohort were used. Eligibility criteria for this control

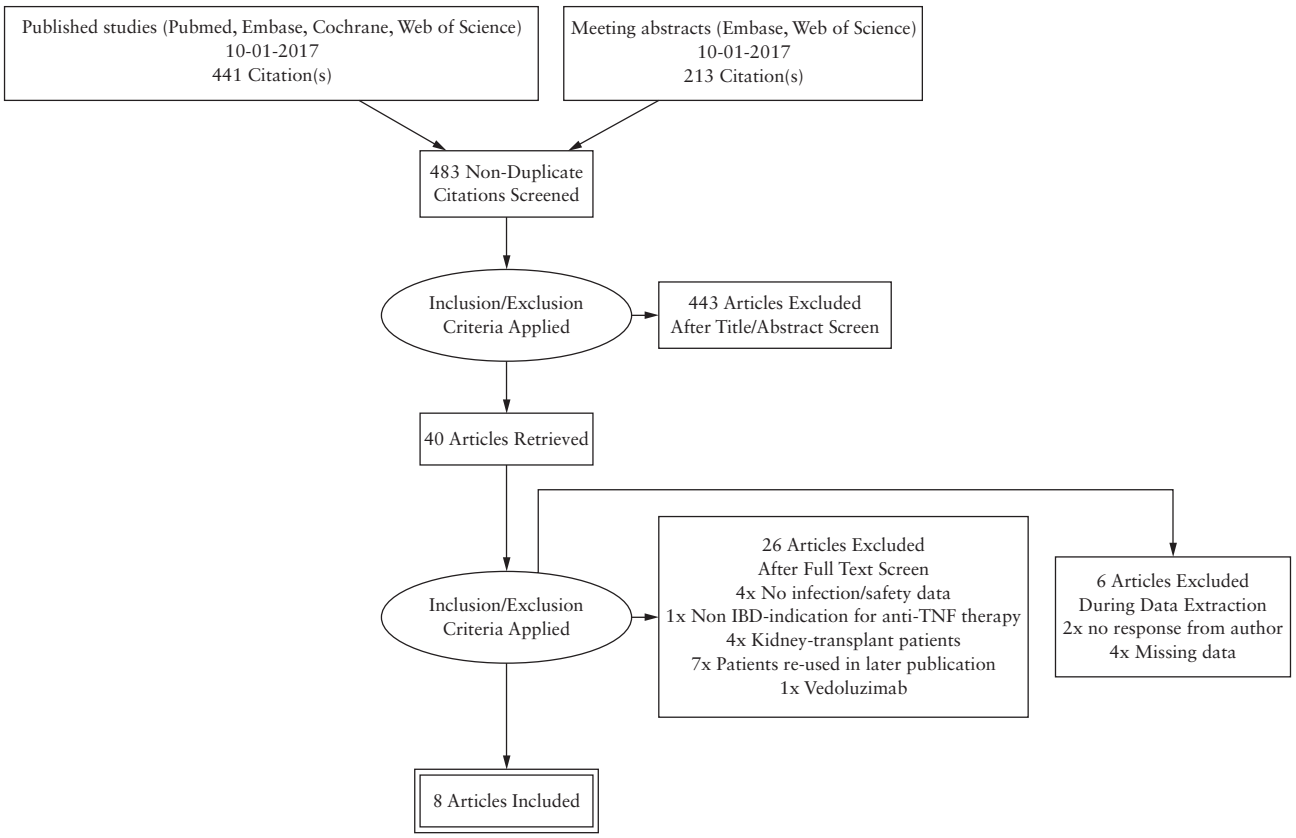

Figure 1. Flow chart of search strategy.

group were: liver transplant in history; alive 6 months post-transplant; IBD diagnosis; and no current or previous anti-TNF-therapy.

2.3. Data extraction

Two authors independently extracted the following patient and control data from each paper: author, year, study type, number of patients, patient age, number and type of infections, follow-up time, and time since transplant, using standard extraction forms. Serious infections were defined according to the serious adverse event definition of the International Conference on Harmonisation [ICH] guidelines for clinical safety data management.[10]

If data was missing from a paper, the authors were contacted to obtain this missing data. The same patient data was extracted from patient records for the LUMC control group, after consent from the Leiden University medical Center [LUMC] ethics committee [MEC number G16-004]. Follow-up of LUMC patients started 6 months after [re-]transplant, to correct for the transplantation surgery-related increased infection rate, and ended at death or study end.

2.4. Quality assessment

Two authors independently assessed the risk of bias in all eligible studies. All studies were appraised using the adapted Newcastle-Ottawa Scale [NOS], which contains nine criteria for cohort studies and is adapted to six criteria for case series and case reports.[11]

To assess the risk of outcome-reporting bias, all studies were scanned for statements about inclusion of all patients within our inclusion criteria as opposed to statements of patient selection.

2.5. Data synthesis and analysis

The patient data waereanalysed using Poisson regression models, with a scale parameter to allow for heterogeneity between studies and with the natural logarithm of the total number of years of follow-up as offset variable, to allow for the between-studies differences in total time at risk. This modelling applies inverse variance weighting and calculates a combined serious infection rate per patient-year [PY] for the anti-TNF group and the control group, resulting in a rate ratio of the two serious infection rates.

Before the analysis, possible confounders were considered. Time between transplant and the start of follow-up, and patient age, were considered factors that could potentially affect serious infection rate and therefore cause confounding in our analysis. To solve this, additional analyses were performed with these factors as covariables. Data were analysed using SPSS v23.

3. Results

Figure 1 describes the search strategy. Initially 465 articles and conference proceedings were found, of which 28 citations were deemed potentially relevant. Finally, eight papers were included in the analysis. Both reviewers agreed on the final selection of these studies.

Table 1. Data of liver transplant recipients on anti-TNF treatment, extracted from papers included in the analysis.

Authors	N	Mean age [years] at start of follow-up	Number of serious infections [type of infection]	Concomitant immunosuppression [n cases]	Mean years follow-up/patient	Study type	NOS checklist
Mohabbat[16]	8	42 [22–69]	4 [*C. diff.*, cryptosporidiosis, EBV, community-acquired pneumonia]	6 tacrolimus 2 cyclosporine	0.9	Case series	5/6
Sandhu[17]	6	49 [28–65]	0	5 tacrolimus 4 cellcept 1 azathioprine 3 prednisone	1.5	Case series	5/6
Indriolo[18]	4	38.5 [22–54]	0	3 tacrolimus 1 azathioprine 1 cyclosporine 1 sirolimus 1 prednisone	1.5	Case series	5/6
Combes *et al.*[19]	18	37.2 [24–51.9]	7 [2 x *C. diff.*, 1 x *E. faecalis* septicaemia, CMV, digestive cryptosporidiosis, chronic HEV 1 x recurring cholangitis]	17 tacrolimus 1 cyclosporine 8 cellcept	1.95	Abstract ECCO, case series	5/6
Pavlidis[20]	6	49 [32,64]	1 [recurrent campylobacter/ norovirus]	6 tacrolimus 1 cellcept 1 azathioprine 3 prednisone	2.2	Letter, case series	5/6
Modiri[15]	9	*39.3*	3 [*C. diff.*, CMV, bactaeremia]		3.86	Cohort study, abstract	7/9
Karolina[21]	1	25	0	1 tacrolimus 1 azathioprine	3.16	Case report	4/6
Lal[22]	1	29	0	1 tacrolimus	0.55	Case report	4/6
Total	51		15		2.2		

NOS, Newcastle-Ottawa Scale; *C. diff.*, *Clostridium difficile* colitis; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HEV, hepatitis E virus infection.

Table 1 shows the total NOS score for each study. None of the studies scored less than 75% of the NOS quality criteria. None of studies received a point on 'demonstration that outcome of interest was not present at start of study', as none reported whether patients had infection at the start of follow-up. It however seems unlikely that anti-TNF therapy was started during a serious infection.

Table 2. Patient characteristics, LUMC cohort [41 patients].

	N
Mean age in years [range]	45 [18–68]
Gender [% male]	70.7
IBD type [%]	
Ulcerative colitis	78.0
Crohn's disease	19.5
Unspecified IBD	2.4%
Indications for LT [%]	
PSC	87.8
PSC & AIH	7.3
Cholangiocarcinoma	2.4
Hepatocellular carcinoma	2.4
Re-graft	17.1
Patient mortality [%]	26.8
Cause of death	
Infection	7.2
Malignancy	9.6
Liver failure	2.4
Other	7.2

LUMC, Leiden University Medical Center; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; AIH, auto immune hepatitis.

From these studies, data were extracted on 53 patients on anti-TNF therapy and 23 control patients not on anti-TNF therapy. Table 1 shows the patient safety data collected for all patients on anti-TNF therapy. No mortalities were reported in any of the study patients.

We identified 41 patients in the LUMC liver transplant cohort who had IBD and underwent LT. Table 2 shows the characteristics for these included patients. Table 3 shows all control patient data.

3.1. Meta-analysis results

As shown in Table 4, the overall infection rate for TNF-exposed patients was 0.168 serious infections per patient-year, which was similar to the 0.149 per year in the control patients [p = 0. 886].

Age at time of transplant was not associated with the rate ratio for serious infections, whereas the time since transplantation was. Although correcting for time since transplant increase, the difference in infection rates between the anti-TNF-group and the control group [0.194 vs 0.115 serious infections per patient-year] the rate ratio remained non-significant [1.70, p = 0.219].

3.2. Sensitivity analysis

We excluded the two case reports, but this did not alter the results. After exclusion of the case reports, time since transplant still influenced [p < 0.001] the infection rates in these groups. The serious infection rate did not differ between groups [p = 0.146].

4. Discussion

This meta-analysis investigated the safety of anti-TNF therapy in liver transplant recipients with IBD. As no randomised controlled trials [RCTs] were available, a cohort study, case series, and case

Table 3. Control patient data from LUMC cohort and studies.

	N	Mean age [years] at start of follow-up	Number of serious infections	Type of infection	Patient-years follow-up
LUMC cohort	41	45.13	69	5 x viral gastroenteritis 9 x [recurring] C=cholangitis 2 x neutropenic fever 12 x pneumonia 2 x spontaneous peritonitis 5 x bacterial gastroenteritis 6 x bacteraemia 7 x CMV infection 4 x sepsis unknown origin 2 x EBV infection 4 x complicated urinary tract infection 1 x *Clostridium* enterocolitis 1 x spondylodiscitis with abscess 1 x sinusitis 2 x fever unknown origin 1 x cellulitis 1 x prostatitis 1 x influenza hospitalisation 1 x perianal abscess 1 x rotavirus hospitalisation 1 x line sepsis	264.3
Modiri	23	42.4	15	MRSA CMV EBV Bacteraemia	278.3
Total	67				

LUMC, Leiden University Medical Center; EBV, Epstein-Barr virus; CMV, cytomegalovirus; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 4. Meta-analysis: serious infection rates and rate ratio for liver transplant recipients exposed and non-exposed to anti-TNF therapy.

Anti-TNFexposed [95% CI]	Non-exposed [95% CI]	Rate ratio	*p*-Value	Correction factor used	*p*-Value
0.168 [0.040–0.710]	0.149 [0.080–0.278]	1.12 [0.233–5.404]	0.886	None	NA
0.127 [0.021–7.67]	0.099 [0.030–0.331]	1.282 [0.257–6.393]	0.762	Age at transplantation	0.423
0.194 [0.094–0.413]	0.115 [0.076–0.172]	1.70 [0.730–3.934]	0.219	Time since transplantation	$p < 0.001$

TNF, tumour necrosis factor; CI, confidence interval; NA, not available.

reports were included. Only one cohort study was identified, so data from the Leiden University Medical Centre liver transplant cohort were used as additional control population.

No difference in the serious infection rate between liver transplant recipients with and without anti-TNF therapy was found. However, as the confidence intervals are wide, this does not fully rule out any clinically significant increase in risk due to addition of anti-TNF therapy. However, in the over 100 patient-years of follow-up during TNF-exposure analysed in this study, no important safety signal was detected. A recent meta-analysis on the safety of anti-TNF therapy in non-transplant IBD patients found no increase in occurrence of serious infections,[12] although other studies found an increase in serious infections after anti-TNF exposure.[6]

The serious infection rate found in our study is substantially higher than the number found in the treat registry of serious infections while using infliximab [15/100 patient-years vs 2.4/100 patient-years]. This is not surprising: in LT recipients, infections are a substantial threat to patient survival. For instance, Daniel *et al*. recently described that 18% of LT recipient mortality is due to infections.[13] Use of anti-TNF therapy does not seem to further increase this risk.

In a study not included in this meta-analysis due to missing data, five patients after LT are treated with infliximab, two of whom develop infectious complications and two develop a post transplant lymphoproliferative disease [PTLD].[14] No clinical benefit was observed in any patient treated with anti-TNF.

The primary limitations of the current analysis are its size and the study types used in the analysis. No RCT and only one cohort study was included. Larger cohort studies would allow for correcting for differences between hospitals or regions in treatment or admission. The only cohort study[15] found no increased risk for infections in the anti-TNF exposed group. In summary, our results suggest that anti-TNF-treatment in combination with LT-associated immunosuppression does not increase the serious infection rate. To further confirm the safety of anti-TNF therapy in post-transplant patients, additional patient data are needed.

Conflict of Interest

None of the authors had a conflict of interest.

Acknowledgments

The authors would like to thank Jan Schoones, library information specialist, for the search strategy.

Author Contributions

MWvM performed the data collection, literature search,d initial statistical analysis, and writing of the paper; BH, AEvdM, RA, GPP, and DS were involved in interpreting the data; and BvH and AI contributed substantially to study design and interpretation of the data. TS contributed to study design, data interpretation, and performing and designing statistical analysis. PWJM contributed to data collection and literature search, study design, interpreting data and data analysis, writing of the paper, and supervision of the project.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012;**56**:1181–8.
2. Adam R, Karam V, Delvart V, *et al*.; all contributing centers [www.eltr.org]; European Liver and Intestine Transplant Association [ELITA]. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry [ELTR]. *J Hepatol* 2012;**57**:675–88.
3. Loftus EV Jr, Sandborn WJ, Lindor KD, Larusso NF. Interactions between chronic liver disease and inflammatory bowel disease. *Inflamm Bowel Dis* 1997;**3**:288–302.
4. Singh S, Loftus EV Jr, Talwalkar JA. Inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. *Am J Gastroenterol* 2013;**108**:1417–25.
5. Rutgeerts P, Sandborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
6. Singh JA, Wells GA, Christensen R, *et al*. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;**16**:CD008794.
7. van Hoek B, de Rooij BJ, Verspaget HW. Risk factors for infection after liver transplantation. *Best Pract Res Clin Gastroenterol* 2012;**26**:61–72.
8. Daniel KE, Eickhoff J, Lucey MR. Why do patients die after a liver transplantation? *Clin Transplant* 2017;**31**. doi: 10.1111/ctr.12906. [Epub Feb 6, 2017.]
9. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.
10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Expert Working Group. *ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. E2A*, 1994. https://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guidelinepdf. Accessed January 10, 2017.
11. Wells GA Shea B, O'Connell D, *et al*. *The Newcastle-Ottawa Scale [NOS] for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. 2011.http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 10, 2017.
12. Bonovas S, Fiorino G, Allocca M, *et al*. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol* 2016;**14**:1385–97.e10.
13. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet* 2007;**369**:1641–57.
14. Parekh P, Segovia M, Kaur N. Tumor-necrosis-factor-α antagonist therapy for inflammatory bowel disease after liver transplantation. ATC abstracts. *Am J Transplant* 2016;**16** [Suppl 3]:2016.
15. Modiri AN, Naik AS, Rizvi S, Zadvornova Y, Stein D. Inflammatory bowel disease patients with solid organ transplants who require anti-TNF

therapy are not at increased risk of serious infections. *Gastroenterology* 2015;**148**:S61.
16. Mohabbat AB, Sandborn WJ, Loftus EV Jr, Wiesner RH, Bruining DH. Anti-tumour necrosis factor treatment of inflammatory bowel disease in liver transplant recipients. *Aliment Pharmacol Ther* 2012;**36**:569–74.
17. Sandhu A, Alameel T, Dale CH, Levstik M, Chande N. The safety and efficacy of antitumour necrosis factor-alpha therapy for inflammatory bowel disease in patients post liver transplantation: a case series. *Aliment Pharmacol Ther* 2012;**36**:159–65.
18. Indriolo A, Fagiuoli S, Pasulo L, Fiorino G, Danese S, Ravelli P. Letter: infliximab therapy in inflammatory bowel disease patients after liver transplantation. *Aliment Pharmacol Ther* 2013;**37**:840–2.
19. Combes R, Altwegg R, Laharie D, *et al*. Efficacy and safety of anti-TNF therapy for inflammatory bowel disease [IBD] in liver transplant recipients for primary sclerosing cholangitis [PSC]: a multicenter experience. *J Crohns Colitis* 2015;**9**:S40.
20. Pavlidis P, Potts J, Barnabas A, *et al*. Anti-tumour necrosis alpha treatment in primary sclerosing cholangitis associated inflammatory bowel disease post liver transplantation. *Liver transpl* 2015; 21:1455.
21. Karolina S, Chetan M. *A unique case of biologic therapy for IBD post liver transplant. Inflammatory bowel diseases*. In: Advances in Inflammatory Bowel Diseases. Crohn's and Colitis Foundation's National Clinical and Research Conference: December 2014; Orlando, FL.
22. Lal S, Steinhart AH. Infliximab for ulcerative colitis following liver transplantation. *Eur J Gastroenterol Hepatol* 2007;**19**:277–80.