



Original Article

Vedolizumab Therapy is Ineffective for Primary Sclerosing Cholangitis in Patients With Inflammatory Bowel Disease: A GETAID Multicentre Cohort Study

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Abstract

Background: Whether vedolizumab may be effective as a treatment for primary sclerosing cholangitis [PSC] in patients with inflammatory bowel disease [IBD] remains controversial.

Methods: We performed a retrospective observational study of consecutive patients with IBD and PSC, treated with vedolizumab for at least 30 weeks in 22 centres of GETAID from January 2015 to June 2016. The outcomes included a decrease in the serum alkaline phosphatase [ALP] concentration of at least 50% from baseline to Week 30 or 54, a change in any serum liver enzymes concentrations, and an assessment of the efficacy and safety of vedolizumab in IBD.

Results: Among 75 patients with active IBD and PSC treated with vedolizumab, 21 patients discontinued vedolizumab before Week 30 [due to lack of efficacy in 19 and malignancy in two patients]. In the remaining 54 patients, a decrease in the serum ALP concentration of at least 50% from baseline to Weeks 30 and 54 was observed in four [7%] and four [11%] patients, respectively. No significant change was observed in serum liver enzyme concentrations at week 30 or 54. After a median follow-up period of 19.4 [14.0–29.9] months, nine cases of digestive neoplasia [colorectal neoplasia in seven and cholangiocarcinoma in two] were reported.

Conclusions: In patients with IBD and PSC, vedolizumab did not improve serum liver enzyme concentrations at week 30 or 54. Nine cases of digestive cancer occurred during the follow-up period, confirming the need for a tight surveillance programme in this population.

Key Words: Crohn's disease; ulcerative colitis; inflammatory bowel disease; vedolizumab; primary sclerosing cholangitis

1. Introduction

Primary sclerosing cholangitis [PSC] is an idiopathic and progressive cholestatic liver disease characterised by persistent biliary inflammation and fibrosis that occur concurrently with IBD in up to 80% of cases.^{1,2} The natural history of PSC is dominated by the risk of biliary stenosis, which can lead to acute cholangitis and/or liver failure secondary to biliary obstruction, and an increased risk of developing digestive neoplasia, such as cholangiocarcinoma, with a 400-fold increased risk of cholangiocarcinoma and a 10-fold increased risk of colorectal cancer.^{2,3}

There is no effective medical therapy for patients with PSC. Although ursodeoxycholic acid is commonly used in patients with PSC, resulting in reduced and even normal serum liver enzymes, ursodeoxycholic acid failed to demonstrate any improvement in the survival of patients with PSC or any decrease in the risk of associated complications.^{4,5} It has been hypothesised that activated T cell homing from the intestine to the liver might be responsible for PSC-associated biliary inflammation through the upregulation of the adhesion molecule MAdCAM-1 and the chemostatic protein CCL, which may contribute to the recruitment of $\alpha 4\beta 7$ integrin-positive T cells to the biliary endothelium.^{6–11}

Vedolizumab is a fully humanised monoclonal antibody that specifically blocks $\alpha 4\beta 7$ integrin-positive leukocyte migration into the inflamed intestinal tissue, thus making it an attractive treatment for IBD patients with concomitant PSC.¹² The efficacy of vedolizumab for PSC in patients with IBD has only been reported in two retrospective studies that included 34 and 27 patients with IBD and PSC, respectively.^{13,14} Due to the relatively small sample sizes and short-follow-ups [few data beyond Week 30], no definite conclusions can be made from these studies.

We therefore decided to evaluate the efficacy of vedolizumab on serum liver enzyme concentrations, as well as its long-term safety, at Weeks 30 and 54 of treatment in consecutive patients with IBD and PSC who were treated in the centres of the Groupe d'Etude

Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID].

2. Methods

2.1. Study population

This was a retrospective observational multicentre study conducted in 22 French and Belgian academic centres affiliated with GETAID. From January 2015 to June 2016, all consecutive adult patients with both IBD and PSC, who received at least one injection of vedolizumab, were included. Diagnosis of PSC was confirmed by two of the following criteria after exclusion of other cholestatic disorders: [1] chronic cholestatic liver disease of at least 6 months duration; [2] intrahepatic and/or extrahepatic biliary duct changes, such as beading or narrowing consistent with PSC as demonstrated by magnetic resonance cholangiography; and [3] liver biopsy compatible with the diagnosis of PSC.¹⁵ Exclusion criteria were: age <18 years; PSC without IBD; inactive Crohn's disease [CD] (Harvey-Bradshaw Index [HBI] <4) or ulcerative colitis [UC] [partial Mayo score <3]; and pregnancy or lactation.^{16,17} Vedolizumab was administered intravenously at a dose of 300 mg at Weeks 0, 2, and 6, and then at a dose of 300 mg every 8 weeks up to Week 54. The optimisation of vedolizumab therapy at a dose of 300 mg every 4 weeks was allowed for insufficient response according to the investigator's decision. The concomitant use of steroids and/or immunomodulators for IBD and ursodeoxycholic acid for PSC was allowed according to the investigator's decision and was recorded at every visit.

The protocol was approved by both the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé [CCTIRS N°15.888] and the Commission Nationale de l'Informatique et des Libertés [CNIL N°916021]. All authors had access to the study data and reviewed and approved the final manuscript.

2.2. Data collection

Investigators from each participating centre were asked to complete a standardised questionnaire. An on-site visit was then conducted to collect missing data from patient case records. The recorded data included patient demographics, a detailed account of the IBD and PSC diagnoses and history, smoking status, IBD phenotype according to the Montreal classification, medical and surgical treatment history, and any serious infection history.

All included patients were followed according to routine practice. At each vedolizumab infusion, patients were assessed by physical examination, and the HBI or partial Mayo score was calculated for patients with CD and UC, respectively. In addition, routine laboratory tests were conducted, which included the following serum liver enzymes: alkaline phosphatase [ALP, international units [UI]], alanine aminotransferase [ALT, UI], aspartate aminotransferase [AST, UI], γ -glutamyltransferase [γ -GT, UI] and total bilirubin [μ mol/L]; C-reactive protein [CRP, mg/L] and haemoglobin [g/dL] levels, as well as leukocyte [10^9 /L] and platelet [10^9 /L] counts and serum albumin [g/L], were determined and evaluated for adverse events.^{16,17} Evaluations of clinical disease activity and liver tests were collected at Weeks 0, 6, 14, 22, 30, and 54. All adverse events occurring during the follow-up period were collected. Severe adverse events were defined as the occurrence of treatment interruption, hospitalisation, disability, persistent damage, colectomy, or death.

2.3. Outcome measures

The primary efficacy endpoint was the effectiveness of vedolizumab in PSC, as defined by a decrease in the serum ALP concentration of at least 50% from baseline to Week 30 or 54. The percentage of patients with a serum ALP concentration lower than 1.5 times the upper limit of normal [ULN] was also calculated. Changes in the total bilirubin, ALT, AST, γ -GT, CRP, and serum albumin concentrations were evaluated at Weeks 30 and 54 compared with Week 0. All adverse events occurring during the follow-up period were also collected. Clinical remission of IBD was defined as an HBI score of 4 or less for CD patients, and a partial Mayo Clinic score of less than 3 with a combined stool frequency and rectal bleeding subscore of 1 or less for UC.

2.4. Statistical analysis

The data were expressed as a number [%] for qualitative data and as the mean \pm standard deviation [SD] or median [interquartile range] for quantitative data. Liver enzymes were expressed according to the upper limit of normal [ULN]; p -values less than 0.05 were considered significant. Efficacy analyses were performed in patients who received vedolizumab for at least 30 weeks, and a safety analysis was performed in all patients who received at least one infusion of vedolizumab. Pre-treatment and post-treatment laboratory tests and clinical indices were compared between Week 0 and Weeks 30 and 54. The proportion of patients with a decrease in ALP concentration of at least 50%, as well as the proportion of patients with serum ALP concentration >1.5 ULN, was compared between Week 0 and Weeks 30 and 54. Nominal and ordinal data were compared using the chi square test or Fisher's exact test, as appropriate, whereas parametric data were compared using the Mann-Whitney test and the Wilcoxon matched-pair signed-rank test as appropriate. All analyses were two-tailed, and p -values less than 0.05 were considered significant. All statistical evaluations were performed using SPSS statistical software [SPSS Inc., v17, Chicago, IL, USA].

3. Results

3.1. Study population

A total of 75 patients with IBD [49 with UC and 26 with CD] and PSC received at least one injection of vedolizumab and were included in the present study [Table 1]. Nineteen patients were treated for less than 30 weeks due to lack of efficacy in IBD, and two discontinued vedolizumab therapy between Week 2 and Week 6 after cholangiocarcinoma was diagnosed. These 21 patients were excluded from the analysis of the efficacy of vedolizumab in PSC [Figure 1]. The remaining 54 patients were treated with vedolizumab for at least 30 weeks and were included in the efficacy analysis [Supplementary Table 1, available as Supplementary data at ECCO-JCC online]. All 75 patients were included in the safety analysis [Table 1].

The demographics, baseline disease characteristics, and medication history of the 75 patients are listed in Table 1. In the overall population [$n = 75$], the median duration of IBD and PSC was 6.2 [3.7–13.5] and 2.9 [0.4–6.6] years, respectively. All patients had active disease at the time of the enrolment, according to the HBI for CD patients [8.0 ± 4.4] and the total Mayo score for UC patients [7.0 ± 2.7]. Most of the patients had been previously treated for IBD with immunosuppressant [89%] and anti-tumour necrosis factor [TNF] [91%] therapy for IBD. Most of the patients had uncomplicated PSC, with the exclusion of three patients with previous liver transplantation and subsequent PSC recurrence, one patient with a history of gallbladder carcinoma, and one patient with a right colon carcinoma. The two patients with a history of digestive neoplasia had been in remission for at least 5 years [Table 1].

At baseline, patients were treated with vedolizumab alone in 29 [39%] cases [Table 1]. Vedolizumab was given with concomitant steroid therapy in 38 [51%] cases and concomitant immunosuppressant therapy in 23 [31%] cases; 65 patients [87%] were also treated with long-term ursodeoxycholic acid at Week 0 at a dose that did not change throughout the study period. Among patients who were not on ursodeoxycholic acid at baseline, none were treated with ursodeoxycholic acid throughout the study period. The effectiveness of vedolizumab on clinical disease activity of IBD is reported in Table 2 and in Supplementary Tables 2 and 3, available as Supplementary data at ECCO-JCC online.

3.2. Effect of vedolizumab on serum liver enzymes

The effectiveness of vedolizumab on serum liver enzymes was assessed in the 54 patients who were treated for at least 30 weeks. Serum liver enzyme concentrations before and after vedolizumab therapy across these 54 patients are shown in Table 2 and Figure 2. There was no significant change in the serum ALP concentration between Week 0 and Weeks 30 or 54 [2.2 ± 2.3 ULN vs 2.3 ± 2.4 ULN and 2.3 ± 2.2 ULN, $p = 0.66$ and 0.98 , respectively], as well as no significant change in other serum liver enzymes concentrations between Week 0 and Weeks 30 or 54. The proportion of patients with an elevated serum ALP concentration [>1.5 ULN] was 37%, 50%, and 46% at Weeks 0, 30, and 54 [$p = 0.24$ and 0.52], respectively. The proportion of patients with a decrease in the baseline serum ALP concentration of at least 50% was 7% and 11% at weeks 30 and 54, respectively [Table 2 and Figure 2].

We next analysed the effectiveness of vedolizumab on the serum liver enzyme concentrations in patients with an elevated serum ALP concentration at Week 0 and in the subgroup of patients with normal serum ALP concentration at Week 0 [Supplementary Tables 2 and 3, available as Supplementary data at ECCO-JCC online].

Table 1. Demographics, disease characteristics, and medication histories of 75 patients of patients with primary sclerosing cholangitis and inflammatory bowel disease treated with vedolizumab.

Characteristic	Crohn's disease [<i>n</i> = 26]	Ulcerative colitis [<i>n</i> = 49]
Median age at IBD diagnosis, years	20.9 [16.6–34.2]	
Median age at PSC diagnosis, years	26.0 [18.3–38.4]	
Male gender, <i>n</i> [%]	51 [68.0%]	
Body mass index, kg/m ²	22.0 ± 3.7	
Median duration of IBD, years	6.2 [3.7–13.5]	
Median duration of PSC, years	2.9 [0.4–6.6]	
Current smoker, <i>n</i> [%]	7 [9%]	
Clinical disease activity scoring	Harvey-radshaw Index 8.0 ± 4.4	Mayo Clinic score 7.0 ± 2.7 Partial Mayo Clinic score 4.9 ± 2.3
Disease location—Montreal classification	L1: 5 [19%] L2: 6 [23%] L3: 15 [58%] L4: 0	E1: 0 E2: 3 [8%] E3: 45 [92%]
Disease phenotype—Montreal classification	B1: 19 [73.1%] B2: 3 [11.5%] B3: 4 [15.4%] p: 6 [8.0%] 12 [46.2%]	- - - - 0
History of intestinal resection, <i>n</i> [%]		
PSC-related symptoms		
Pruritus		3 [6%]
Right upper quadrant abdominal pain		2 [3%]
Jaundice		2 [3%]
Ascites		1 [1%]
Splenomegaly		3 [4%]
Hepatomegaly		6 [8%]
Asymptomatic		65 [87%]
History of IBD treatment, <i>n</i> [%]		
Aminosalicylates		62 [83%]
Steroids		73 [97%]
Immunosuppressant		67 [89%]
Anti-TNF therapy		68 [91%]
Biological variables		
Alkaline phosphatase [ULN] [normal <120]		2.0 ± 2.6
ALP > 1.5 ULN, <i>n</i> [%]		27 [36%]
Aspartate aminotransferase [ULN] [normal <40]		1.4 ± 1.1
Alanine aminotransferase [ULN] [normal <40]		1.7 ± 1.8
γ-glutamyltransferase [ULN] [normal <40]		5.3 ± 8.3
Total bilirubin [ULN] [normal <17]		1.1 ± 1.7
Serum albumin [g/L] [normal >35]		36.7 ± 5.2
Platelet count, 10 ⁹ /L		342 ± 162
hsCRP level, mg/L		15.8 ± 21.9
Concomitant medications		
Glucocorticoids		38 [51%]
Immunosuppressants		23 [31]
Ursodeoxycholic acid		65 [87%]

ALP, alkaline phosphatase; hsCRP, high sensitivity C-reactive protein; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; ULN, upper limit normal; TNE, tumour necrosis factor.

Variables are presented as *n* [%], mean ± standard deviation, or median [interquartile range].

Of the 20 patients with elevated serum ALP concentration at baseline, two patients had a decrease of at least 50% of the baseline serum ALP concentration at Weeks 30 and 54 [10% and 13.3%, respectively] [Supplementary Table 2]. Overall, there was no significant change in any liver enzyme concentration between Week 0 and Weeks 30 or 54 in patients with an elevated serum ALP concentration at Week 0.

Of the 34 patients with a normal serum ALP concentration at baseline, two patients had a decrease of at least 50% of the baseline

serum ALP concentration at Weeks 30 and 54 [6% and 9%, respectively] [Supplementary Table 3]. Overall, there was no significant change in any liver enzymes between Week 0 and Weeks 30 or 54 in patients with normal serum ALP concentration at Week 0, with the exception of one patient with a significant increase in the serum ALP concentration at Week 30 but not at Week 54. The proportion of patients with an elevated serum ALP concentration [>1.5 ULN] was 27%, and 23% at weeks 30 and 54 [*p* = 0.002 and 0.02], respectively.

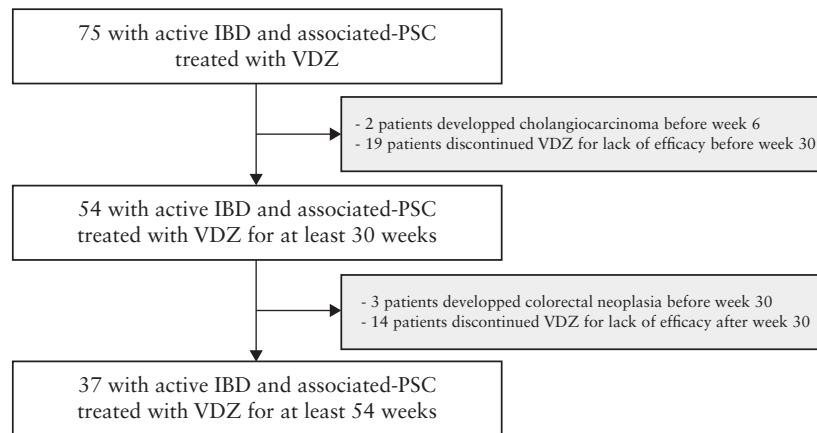


Figure 1. Flow chart of patient with inflammatory bowel disease with primary sclerosing cholangitis, treated with vedolizumab from Week 0 to Week 54.

Table 2. Changes in laboratory tests and clinical scoring at Weeks 30 and 54 in patients with primary sclerosing cholangitis and inflammatory bowel disease, treated with vedolizumab.

	Changes between Week 30 and Week 0 [n = 54]	p	Changes between Weeks 54 and 0 [n = 37]	p
Alkaline phosphatase, ULN	0.1 ± 1.7	0.66	-0.01 ± 2.4	0.98
Aspartate aminotransferase, ULN	0.1 ± 1.2	0.58	-0.2 ± 0.9	0.33
Alanine aminotransferase, ULN	-0.01 ± 1.9	0.96	-0.4 ± 1.5	0.22
γ-glutamyltransferase, ULN	-0.3 ± 1.6	0.17	-0.4 ± 0.36	0.31
Total bilirubin, ULN	0.5 ± 5.0	0.51	0.1 ± 5.4	0.84
Serum albumin, g/L	2.3 ± 7.7	0.06	-0.5 ± 10.0	0.01
Platelet count, 10 ⁹ /L	-27 ± 106	0.02	-43 ± 163	0.03
hsCRP level, mg/L	-5.6 ± 20.2	<0.001	-0.5 ± 10.0	0.16
Harvey-Bradshaw index	-3.1 ± 6.0	0.03	-4.2 ± 6.5	0.04
Partial Mayo Clinic score	-2.0 ± 2.6	<0.001	-2.9 ± 3.0	<0.001

CRP, C-reactive protein; ULN, upper limit of normal.

3.3. Effect of vedolizumab on activity of the inflammatory bowel disease

All 54 patients were assessed for clinical activity at Week 30 and 37 at Week 54. Seventeen patients discontinued vedolizumab between Weeks 30 and 54 for lack of response in 14 cases and after colorectal neoplasia were diagnosed in three cases.

Among the 33 patients with UC, steroid-free clinical remission was achieved in 42%, 48%, and 50% at Weeks 14, 30, and 54, respectively. Among the patients with UC, 27 [82%] were assessed for mucosal healing between Week 30 and Week 54. According to the Mayo Clinic endoscopic subscore [0 or 1], mucosal healing was achieved in 11 [42.3%].

Among the 21 patients with CD, steroid-free clinical remission was achieved in 43%, 48%, and 46% at Weeks 14, 30, and 54, respectively. Among the patients with CD, seven [33.3%] were assessed for mucosal healing between Weeks 30 and 54, of whom three [42.9%] achieved mucosal healing [absence of ulcer].

No difference was found in the impact of vedolizumab on clinical activity of IBD according to the level of serum ALP concentration at Week 0 [Supplementary Table 4 available as Supplementary data at ECCO-JCC online]. Patients with elevated serum ALP concentration at Week 0 had higher CRP level at Weeks 0 and 54 and lower albumin level at Week 54.

3.4. Safety and malignancy risk

The analysis of adverse events was performed in the entire cohort [n = 75] of patients who received at least one dose of vedolizumab.

After a median follow-up period of 1.6 [1.2–2.5] years, 19 adverse events occurred in 19 [25%] patients, including 11 [15%] severe adverse events. These adverse events consisted of infection in 10 cases and digestive neoplasia in nine cases.

The characteristics of the nine patients who developed digestive neoplasia are reported in Table 3. Two cholangiocarcinomas were diagnosed during the vedolizumab induction phase, with symptoms of acute jaundice and cholestasis. One patient subsequently died after not responding to chemotherapy, and the other patient was still alive at the end of the follow-up period but had a progressive disease despite chemotherapy and only received the best supportive care. Three colorectal neoplasias were diagnosed between Weeks 30 and 54. Four additional cases of colorectal neoplasia were diagnosed between 1 and 3 years after the introduction of vedolizumab. Six out of seven cases of colorectal neoplasia were diagnosed during a colonoscopy screening and consisted of high-grade dysplasia or stage 1 adenocarcinoma, whereas one patient presented with an aggressive form of rectal carcinoma and subsequently died.

4. Discussion

The management of IBD-associated PSC remains challenging. Given the limitations of the available studies, we sought to further investigate whether vedolizumab, by inhibiting the recruitment of α4β7 integrin-positive cells within the liver, might be an effective and safe treatment of PSC in patients with IBD.¹² In the 75 patients with PSC and active IBD included in this study, we first evaluated

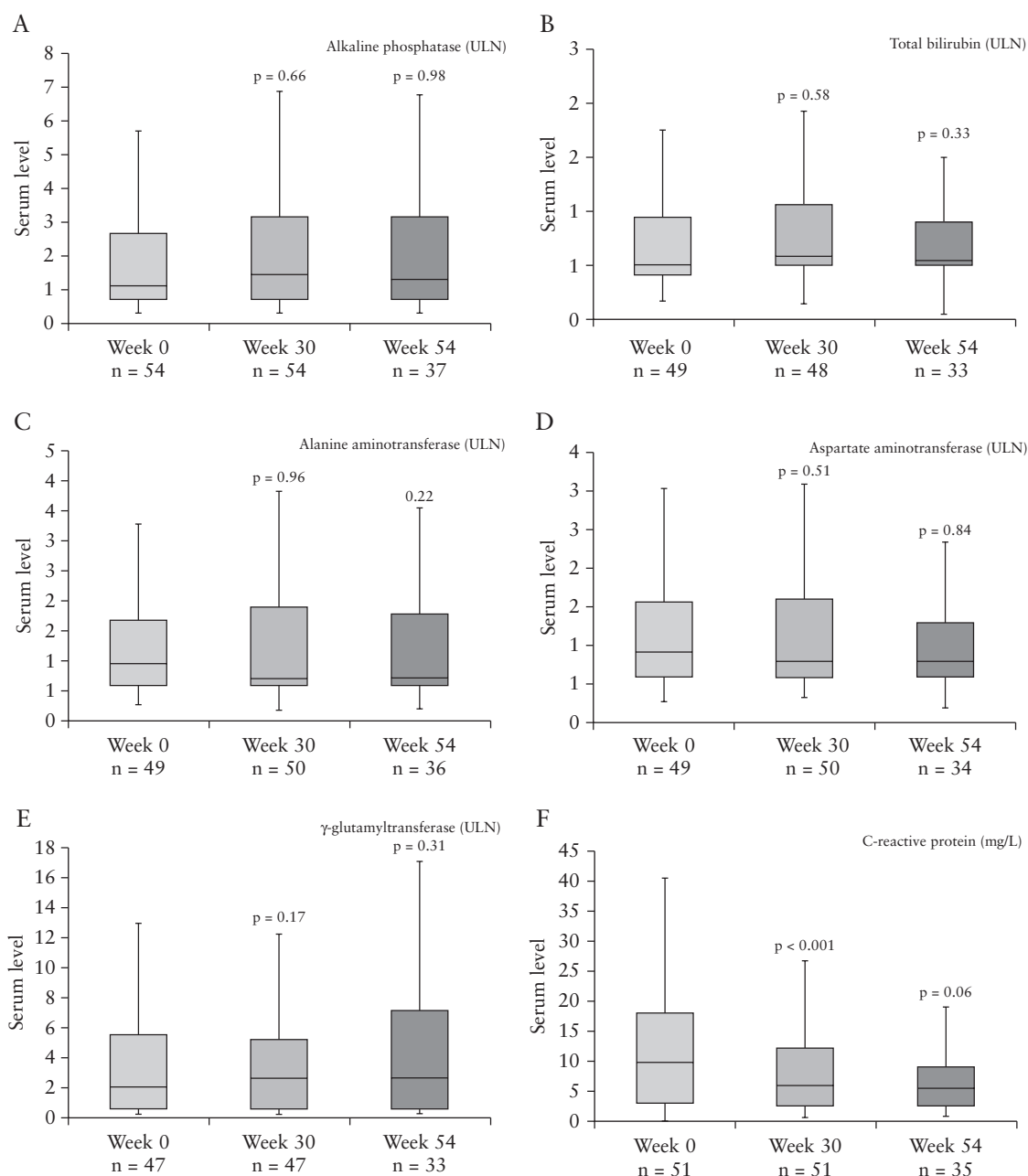


Figure 2. Serum liver enzymes and C-reactive protein concentrations of 54 patients with inflammatory bowel disease, treated with vedolizumab for at least 30 weeks: [A] alkaline phosphatase; [B] total bilirubin; [C] alanine aminotransferase; [D] aspartate aminotransferase; [E] γ -glutamyltransferase; [F] C-reactive protein. In the panels, the horizontal line in each box represents the median, the top, and the bottom of the boxes; the interquartile range; and the bars 1.5 times the interquartile range.

the effectiveness and safety of vedolizumab therapy in 54 patients treated with vedolizumab for at least 30 weeks. Overall, there was no improvement in the liver tests. Only four patients [7.4%] had a decrease in the serum ALP concentration of at least 50% from baseline to Week 30 and Week 54. Even though the safety profile concerning infectious risk was consistent with previous real-world data with vedolizumab, we reported a high rate of digestive neoplasia, especially during the first year of treatment with vedolizumab.^{18,19}

Two retrospective studies have been recently published assessing the effectiveness of vedolizumab on PSC in patients with concomitant IBD and PSC.^{13,14} Christensen *et al.* included 34 patients [16 with CD and 18 with UC] with a serum liver enzyme assessment

at Week 14 and Week 30, and Tse *et al.* included 27 patients [10 with CD and 16 with UC] with a serum liver enzyme assessment at 6–8 months in 23 cases and at 12–14 months in 19 cases. There was no improvement in the ALP concentration or in any serum liver enzyme concentration, despite the clear evidence of clinical effectiveness on IBD activity in the first study. Our study confirmed that vedolizumab was not effective for treating PSC but was clearly effective for treating active IBD. Indeed, there was no change in the ALP concentration or in other serum liver enzyme concentrations. No change in effectiveness in PSC was found by stratifying patients according to an elevated concentration of ALP at baseline. There was no evidence to suggest that the lack of efficacy of vedolizumab in

Table 3. Characteristics of the nine incident cases of digestive neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease, treated with vedolizumab.

Gender, age [years]	Delay between digestive neoplasia and			Type of neoplasia	Vedolizumab therapy at the time of diagnosis of digestive neoplasia	Type, findings, and delay of the last screening test before vedolizumab introduction [months]	Staging	Outcome
	diagnosis of IBD [years]	diagnosis of PSC [years]	introduction of VDZ [months]					
During the induction phase								
M, 32.9	11.3	5.5	1.2	Cholangiocarcinoma	Yes	MRI showing stable multiple intrahepatic stricture without evidence of cancer. 12.2	T2N1M1	Died
M, 51.1	6.7	0.1	1.3	Cholangiocarcinoma	Yes	MRI showing strictures of the left hepatic duct with no evidence of cancer. 2.8	T2N1Mx	Alive, palliative chemotherapy ongoing
During the first year of vedolizumab therapy								
M, 29.2	6,0	3.6	5,9	Colorectal neoplasia	Yes	Colonoscopy showing active pancolitis [MCES 3; UCEIS 5]. No evidence of dysplasia on random biopsies, 6.6	pT2N0M0	Proctocolectomy
M, 44.7	11,0	0.4	6,1	Colorectal neoplasia	Yes	Colonoscopy showing active pancolitis [MCES 3; UCEIS 6]. No evidence of dysplasia on random biopsies, 6.1	pT2N0Mx pT4N1M1	Died
M, 48.2	13,6	12.8	9,7	Colorectal neoplasia	Yes	Colonoscopy showing active pancolitis [MCES 3; UCEIS 4]. No evidence of dysplasia on random biopsies, 5.3	HGD	Proctocolectomy
After the first year of vedolizumab therapy								
M, 36.4	17,5	6.8	14,9	Colorectal neoplasia	Yes	Colonoscopy showing pancolitis [MCES 2; UCEIS 3], 18.4	pT2N0Mx	Proctocolectomy
F, 34.0	20,4	17.4	35,8	Colorectal neoplasia	Yes	Colonoscopy showing pancolitis [MCES 2; UCEIS 3], 16.4	pT1N0Mx	Proctocolectomy
F, 27.5	5,2	3.3	22,5	Colorectal neoplasia	Yes	Colonoscopy showing active proctitis [MCES 3; UCEIS 6] and inactive colitis [MCEIS 1; UCEIS 2], 22.5	HGD	Proctocolectomy
M, 23.8	8,9	0.2	33,6	Colorectal neoplasia	Vedolizumab discontinued after 16.1 months	Colonoscopy showing active pancolitis [MCES 3; UCEIS 6]. No evidence of dysplasia on random biopsies, 21.4	HGD	Proctocolectomy

All screening colonoscopies were complete and performed with a 4-litre polyethyleneglycol preparation and indigo carmine chromoendoscopy.

F, female; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; M, male; MCES, Mayo Clinic Endoscopic Subscore; PSC, primary sclerosing cholangitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; VDZ, vedolizumab.

PSC was related to a lack of efficacy of vedolizumab in IBD. Indeed, the effectiveness of vedolizumab in IBD was in line with previous reports in patients with IBD and without PSC.¹⁹

In the present study, infection was the most frequent adverse event, and there were only two serious adverse events of infection. Importantly, nine cases of digestive neoplasia were reported following a median follow-up of 19.4 months. Previous reports in this patient population did not identify such a risk. However, the duration of follow-up and the sample size were smaller in previous reports than in this nationwide GETAID study. In particular, five cases of digestive neoplasia were reported in patients with IBD and PSC treated with vedolizumab during the first year of treatment, comprising two cases of cholangiocarcinoma and three cases of colorectal cancer. An additional safety survey focusing on the occurrence of digestive neoplasia was therefore set up, which identified four additional cases with a median follow-up period of 1.6 [1.2–2.5] years. Whether this malignancy risk is related to the impairment of the immunosurveillance of the gastrointestinal [GI] tract induced by anti-integrin antibodies, or to the well-known increased risk of malignancy in patients with both IBD and PSC, will require further investigation.

All the patients included in this study had no evidence of colorectal neoplasia on colonoscopy before enrolment. All the patients with incidental colorectal neoplasia had undergone a complete screening colonoscopy, with indigo carmine chromoendoscopy, with a delay of 5.3 to 22.5 months before the introduction of vedolizumab. The majority of patients had endoscopically active disease, which may have biased screening performance. Similarly, the two patients who developed cholangiocarcinoma had magnetic resonance imaging [MRI] assessment before enrolment that showed no evidence of cholangiocarcinoma. Indeed, the risk of cholangiocarcinoma among patients with PSC is 400 times higher than the risk in the general population.^{2,20} Similarly, the risk of colorectal cancer among patients with PSC and IBD is four times higher than the risk among patients with IBD alone, and 10 times higher than the risk in the general population.^{2,21} Although the two patients who were diagnosed with cholangiocarcinoma presented with a rapidly progressive disease, the occurrence of cancer was noted during the induction phase, suggesting a potential underlying pre-neoplastic lesion. The other cases of colorectal neoplasia occurred in patients who had entered a mandatory tight screening programme with various onset delays after the introduction of vedolizumab. No similar safety signal was reported in the study of Christensen *et al.*,²² whereas no safety data are available in the study of Tse *et al.*^{13,14}

A meta-analysis estimated the likelihood of experiencing malignancy when patients with IBD without PSC were administered anti-integrin antibodies or a placebo.²² Among the 1146 patients randomised to receive gut-specific anti-integrin antibodies, there were three [0.3%] malignancies compared with two [0.3%] malignancies among the 664 receiving placebo (risk ratio [RR] = 0.78; 95% confidence interval [CI] 0.15–4.02), with no heterogeneity between studies. In another review, malignancy was reported in 18/2830 IBD patients with vedolizumab exposure compared with 1/504 in placebo-exposed patients with IBD.²³ Six out of 18 of the vedolizumab-exposed patients had gastrointestinal malignancies [three colorectal cancers, one hepatic cancer, one appendiceal carcinoid metastasis, and one peritoneal metastasis], which were diagnosed after a median [range 2–41] vedolizumab infusions.

We acknowledge several limitations to the present study due to its retrospective design. However, this study also has several strengths. First, we provide efficacy data up to Week 54, a significantly longer

period than that of previous studies; therefore, this study is probably more appropriate to demonstrate any significant improvements in the liver tests. Second, the sample size for such a patient population is considered clinically relevant. Third, this was a nationwide survey of consecutive patients. Finally, a long-term follow-up allowed us to explore the safety profile of vedolizumab in this specific population.

In conclusion, vedolizumab was not effective to change serum liver enzyme concentrations in patients with IBD and PSC, despite clear evidence of its effectiveness in active intestinal inflammation. Moreover, we reported an unexpected number of digestive neoplasia cases that might be attributable to impaired immunosurveillance induced by vedolizumab therapy but may also be related to the well-known increased risk of malignancy in this patient population. Overall our findings, together with previous reports, are not in favour of conducting a controlled trial on vedolizumab in PSC. Close monitoring of patients with both IBD and PSC, who have been treated with vedolizumab, is recommended in routine practice, using yearly colonoscopy screening and MRI.

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Conflict of Interest

LP-B has received consulting fees from Merck, Abbvie, Janssen, Genentech, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-Pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, Pfizer, and HAC-Pharma. This author has also received lecture fees from Merck, Abbvie, Takeda, Janssen Cilag, Ferring, Norgine, Tillots, Vifor, Therakos, HAC-Pharma, and Mitsubishi. BP has received consulting fees from Abbvie, MSD, and Pfizer. This author has also received speaking fees from Abbvie, MSD, Ferring, and Takeda. YB has received lecture and consulting fees from Abbvie, Biogaran, Boehringer-Ingelheim, CTMA, Ferring, Gilead, Hospira, ICON, Inception IBD, Janssen, Lilly, Mayoli Spindler, Merck, MSD, Norgine, Pfizer, Roberts Clinical Trials, Roche, Sanofi, Shire, Takeda, UCB, and Vifor Pharma. This author has also stock ownership of Inception IBD, San Diego, CA, USA. PS has received consulting fees from Takeda, Abbvie, Merck-MSD, Astellas, Ferring, and Biocodex, grants from Biocodex, sponsored travel from Merck-MSD and Takeda. GB has received consulting fees from MSD, Janssen, and Abbvie. This author has also received lecture fees from MSD, Abbvie, Pfizer, Takeda, and Ferring. DL has received consulting and lecture fees from AbbVie, Ferring, Janssen Cilag, MSD, Pfizer, and Takeda. RA has received board or lectures fees from Abbvie, Janssen, Pfizer, Takeda. CR has received consulting fees, lecture fees, and travel accommodations from AbbVie, Takeda, MSD, Mundipharma, Hospira, and Ferring. CT-P has received lecture fees from MSD, Abbvie, Vifor Pharma, and Norgine. This author has also received travel accommodations from Biogaran, Takeda, Hospira, MSD, and Mayoli Spindler. SN has received consulting fees from Merck, Abbvie, Takeda, Ferring, Norgine, Vifor Pharma, Novartis, Janssen Cilag, Hospira, Takeda, and HAC-Pharma. JF has received lecture and consulting fees from Abbvie, Astellas Pharma, Covidien, Ferring, Jansen, MSD, Pfizer, and Takeda. VA has received lecture fees from Ferring, MSD, Vifor Pharma, and Abbvie. GS has received lecture fees from Vifor Pharma, Takeda, Pfizer, HAC Pharma, Abbvie, MSD, and Ferring France. This author has also received travel accommodations from Ferring, Abbvie, and MSD France as well as a research grant from Ferring. LV has received lecture fees from Abbvie, MSD, Takeda, Ferring, Janssen, and Pfizer, and research grants from MSD, Takeda, and Pfizer. SV has received consulting fees from Abbvie, MSD, Takeda, Vifor Pharma, and Ferring. Mathurin Fumery has received lecture fees from Abbvie, MSD, and Ferring. J-MR has received consulting fees from Hospira. This author has also received lectures fees from Abbvie, Ferring, Janssen, and Takeda. This author has also received travel accommodations from Ferring, Abbvie, MSD, Janssen, Pfizer, Hospira, and Takeda. AA has received consulting fees from Abbvie, Hospira, Takeda, Gilead, and Biocodex, as well as lecture fees and travel accommodations from

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Author Contributions

Concept and design of the study: AA, LPB, BC, JPB, JMR. Generation, collection, assembly, analysis and/or interpretation of data: BC, LPB, BP, YB, PS, GB, LC, DL, FC, RA, CR, MS, CTP, SN, JF, VA, GS, LV, SV, MF, MR, JPB, JMR, AA. Drafting or revision of the manuscript: BC, LPB, BP, YB, PS, GB, LC, DL, FC, RA, CR, MS, CTP, SN, JF, VA, GS, LV, SV, MF, MR, JPB, JMR, AA. Approval of the final version of the manuscript: BC, LPB, BP, YB, PS, GB, LC, DL, FC, RA, CR, MS, CTP, SN, JF, VA, GS, LV, SV, MF, MR, JPB, JMR, AA.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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