Early vedolizumab trough levels at induction in inflammatory bowel disease patients with treatment failure during maintenance

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Background Vedolizumab (VDZ) is effective as an induction and maintenance treatment for Crohn's disease and ulcerative colitis, but, as observed with antitumour necrosis factor-α (anti-TNFα) agents, some patients are nonetheless experiencing loss of response.

Objective The aim of this study was to investigate the impact of the pharmacokinetics of VDZ during induction on long-term treatment response.

Patients and methods This study focused on a single cohort of 103 inflammatory bowel disease patients treated with VDZ. VDZ trough levels (TLs) were measured by enzyme-linked immunosorbent assay ($n = 536$ samples), and thereafter correlated to clinical, biological, endoscopic and serological data. For patients exposed previously to infliximab, antibodies to infliximab were measured at baseline. On the basis of the outcome at the end of follow-up, patients were then categorized into long-term response, optimized and treatment failure groups.

Results During VDZ induction, at week 6, inflammatory bowel disease patients with long-term response had higher TLs compared with patients in the treatment failure group (33 vs. 24 μg/ml, $P = 0.02$). A cut-off TL of 28 μg/ml predicted a sustained response in the follow-up with an area under curve of 0.723 (95% confidence interval = 0.567–0.878, $P = 0.02$). Patients with mucosal healing in maintenance had higher TLs at week 6 (41.65 μg/ml) compared with patients with mild (26 μg/ml) or severe endoscopic activity (20.8 μg/ml), $P = 0.009$. Positive perinuclear antineutrophil cytoplasmic antibody serology was associated with lower TLs. Patients previously exposed to anti-TNFα had lower TLs than naive patients (22.5 vs. 36 μg/ml, $P = 0.03$) without any impact of detectable antibodies to infliximab. Finally, the presence of an immunomodulator at induction did not impact on VDZ TLs at induction.

Conclusion We confirmed that a drug exposure–efficacy association was found early on at induction. This study emphasizes that previous exposure to anti-TNFα and positive perinuclear antineutrophil cytoplasmic antibody serology are important factors influencing VDZ TLs at induction. Eur J Gastroenterol Hepatol 31:478–485

Introduction

Over the past 2 decades, antitumour necrosis factor-α (anti-TNFα) monoclonal antibodies have improved the treatment of inflammatory bowel disease (IBD). Loss of response (LOR) to anti-TNFα during maintenance in patients who initially responded to treatment induction represents a major challenge in daily practice [1]. Approximately 10–40% of patients will lose response over 12 months of treatment [2,3].

European Journal of Gastroenterology & Hepatology 2019, 31:478–485

Keywords: induction, inflammatory bowel disease, pharmacokinetics, trough level, vedolizumab

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Received 21 September 2018 **Accepted** 10 December 2018

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.eurojgh.com.

Therapeutic drug monitoring (TDM) algorithms in the management of patients losing response to anti-TNFα therapies [4] have been proposed to guide treatment optimization, with some evidence to support their use in practice. Interestingly, several studies [5–7] have now highlighted the interest of measuring infliximab (IFX) trough levels (TLs) at induction to predict the LOR to optimize patients early on. In addition to anti-TNFα, new biological approaches are now rapidly expanding and incorporating our therapeutic armamentarium. Vedolizumab (VDZ), a humanized immunoglobulin G1 monoclonal targeting α4β7 integrin, selectively inhibits the interaction between MadCAM-1 expressed on endothelial cells and α4β7 integrin expressed on lymphocytes. VDZ prevents circulating activated memory T cells from the periphery to infiltrate the intestinal mucosa and perpetuate inflammation. The efficacy of VDZ in IBD has already been shown repeatedly in RCTs and real-world experience studies [8–12]. Similar to anti-TNFα therapies, patients treated with VDZ experience LOR. It is therefore reasonable to evaluate the VDZ pharmacokinetics to the same extent as the anti-TNFα pharmacokinetics in patients losing response. Obviously, their mechanisms of action and pharmacodynamic properties are different, but differences in

pharmacokinetics also exist. The serum half-time of VDZ is around 25 days, whereas the serum half-time of IFX is around 14 days [13,14]. VDZ pharmacokinetics is affected more by target-mediated mechanisms, corresponding to the nonlinear elimination in the two-compartment pharmacokinetic model, than anti-TNFα antibodies, which are mainly eliminated by Fc-receptor-mediated mechanisms, corresponding to a linear clearance [13]. VDZ seems to be less immunogenic than IFX as described by the low occurrence of anti-VDZ antibodies (AVAs) observed in the first trials [8, 11]. Thus, observations on anti-TNFα pharmacokinetics reported so far may not be applicable to VDZ. However, emerging data have already suggested the relevance of measuring TLs early on at induction to predict mucosal healing [15,16], response [16] or need for optimization [17]. In this study, the impact of pharmacokinetics of VDZ at induction on long-term response was examined.

Patients and methods

Study design

This study was carried out in a single centre, at Erasme Hospital, Brussels, Belgium, and received Erasme Hospital Ethic committee approval (P2018/451). The samples were collected prospectively from September 2015 to 31 December 2017 with a retrospective analysis of the clinical data. Treating physicians were not aware of VDZ TL at the time of treatment and treatment management was therefore based on standard of care.

Study population

Overall, 103 patients received VDZ treatment. Twenty-two patients were excluded from analyses for the following reasons: seven patients had a follow-up less than 14 weeks, nine patients were lost to follow-up and six patients stopped VDZ because of side effects [arthralgia ($n=1$), sinusitis ($n=2$), testicular neoplasia ($n=1$), surgery for Crohn's disease (CD) complication ($n=1$) and intense fatigue ($n=1$)]. Finally, 81 patients were considered for the following analyses. Primary nonresponse was defined as a lack of response to VDZ within 14 weeks after the first infusion requiring treatment modification (e.g. steroids, surgery, etc.). Secondary nonresponse was defined as the need for VDZ optimization and/or to swap to other biologics because of new flare-up of disease during treatment after the induction period.

Data collection

Clinical information was collected retrospectively from hospital electronic patient charts that enabled chronological listing of all events. In addition to demographic data, the following data were collected: dates of start and end/discontinuation of VDZ treatment, dates of the three induction regimen infusions, infusion dates during maintenance, dates of changes in the interval of administration, use of concomitant immunomodulator (IMM), dates of any change in escalation or de-escalation of IMM (starting or stopping IMM), type I immediate hypersensitivity, reasons for stopping VDZ [secondary non responder, pregnancy, loss of follow-up, need for surgery, deep remission, the occurrence of adverse events (e.g. infections)] and serologic status for perinuclear antineutrophil cytoplasmic antibody (pANCA), antinuclear antibodies and anti-*Saccharomyces cerevisiae* antibodies.

Active disease was defined on the basis of clinical, biological and endoscopic criteria. Disease activity was evaluated retrospectively by physician's global assessment. Biological activity was assessed when available using serum C-reactive protein (CRP) levels. Endoscopic activity was taken into account if available within the month before VDZ infusion and was divided into three groups: quiescent, mild and severe endoscopic activity. Quiescent endoscopic activity was defined as the absence of endoscopic lesions corresponding to mucosal healing; mild endoscopic activity as the presence of a few superficial ulcerations for CD or subscore endoscopic Mayo = 1–2 for ulcerative colitis (UC); or severe endoscopic activity as the presence of several deep ulcers for CD or subscore endoscopic Mayo = 2–3 for UC. At baseline, 47 endoscopies were available and 42 endoscopies were available between weeks 14 and 54. In this retrospective study, the dates of all clinical, biological and endoscopy data were integrated to consider all disease activity parameters over time. Data collection was stopped on 31 December 2017. The different outcomes described in the study population were reported up to this date.

Blood samples

Blood samples were collected prospectively and serum samples were stored in the Biobank of the Laboratory of Experimental Gastroenterology. This Biobank was approved by the Erasme Hospital Ethic committee and each patient signed an informed consent in accord with ethical guidelines of the 2013 Declaration of Helsinki (EC number B2011/005). We analysed 536 samples issued from 103 IBD patients treated with VDZ.

All patients underwent routine 7 ml blood sample collection at the infusion unit before each new infusion. These samples were centrifuged and the serum was divided into 1000 µl aliquots and stored at – 20°C.

Laboratory methods

All samples were analysed for VDZ TL using an enzyme-linked immunosorbent assay (ELISA). This ELISA kit (apDia bvba, Turnhout, Belgium) was based on microtitrestrips coated with anti-VDZ monoclonal antibody clone 6F3 and a specific peroxidase-conjugated monoclonal antibody (clone 6E6) recognizing VDZ specifically [16]. A standard dilution of 1/400 and 1/100 was used to measure TL at induction and maintenance, respectively. A calibration curve was obtained by plotting the absorbance values versus the corresponding calibrator values. VDZ TLs are expressed as micrograms per millilitre (µg/ml). Antibodies to IFX (ATI) were measured with a drug-sensitive bridging ATI assay, except for four samples, where a drug-tolerant ATI assay was used because of detectable residual IFX TLs [18]. ATI are expressed as nanograms per millilitre (ng/ml).

Statistical analysis

The Mann–Whitney test was used to compare continuous variables between two groups, whereas the Kruskall–Wallis test was used when more than two groups were compared.

Results were expressed as median with interquartile range (IQR). Pearson's χ^2-test was used to compare categorical variables between groups. Univariate and multivariate analyses were carried out by logistic regression after conversion of continuous variables into binary variables. Results were expressed as odds ratios (ORs) and its 95% confidence intervals (CIs). Cox regression was used to compare the cumulative survival without optimization. Significant difference between outcomes was set for P values lower than 0.05. All data were gathered in a central database using Excel (Microsoft, Redmond, Washington, USA) and analysed using SPSS Statistics 23 (Chicago, Illinois, USA).

Results

Study population

Of the 103 enrolled patients in this study, 22 patients were excluded (see Patients and Methods section). Finally, 81 patients were considered including 40 patients with CD) and 41 patients with UC.

In this longitudinal retrospective follow-up, three different outcomes that determined the studied groups were observed: a long-term response group including patients treated successfully with VDZ without LOR [33/81 (40.7%) cohort]; an optimized group including patients experiencing LOR with a secondary response after optimization (interval reduction) [12/81 (14.9%) cohort]; and a treatment failure group including patients with a primary or a secondary failure to VDZ treatment, despite optimization or not, and whether requiring a switch to another class of biologics or surgery [36/81 (44.4%) cohort]. In addition, physician's global assessment, CRP and endoscopy helped to classify disease as quiescent in long-term response and optimized groups and active in the treatment failure group.

Baseline demographics and detailed characteristics of the overall population and the different outcomes are summarized in Table 1. The distribution of CD/UC among outcomes was different, with a predominance of CD patients in both optimized and treatment failure groups and a predominance of UC patients in the long-term response group ($P = 0.02$). A previous surgery was more frequently found in both optimized and treatment failure groups ($P = 0.04$). Similarly, CD patients included in the treatment failure group showed more frequently a complicated phenotype B3 ($P = 0.04$). Proportion of previous use of biologics was similar between groups. By considering only long-term response and treatment failure groups, a higher proportion of patients with previous use of anti-TNFα was found in the treatment failure group ($P = 0.02$). In this latter group, it should be highlighted that 66.6 and 22.2% of patients had previously received two and three anti-TNFα, respectively.

At the end of the data review on December 2017, the median follow-up was significantly different in three outcomes ($P < 0.0001$). The Optimized group had the longer median follow-up, 26 (9–31) months, whereas the treatment failure group had a median follow-up of 6 (1–20) months and long-term responders group had a median follow-up of 11 (3–27) months. The first optimization was required earlier in the treatment failure group [median (IQR): 26 (16–33) weeks] than in the optimized group [median (IQR): 41 (25–76) weeks], $P = 0.038$.

Early vedolizumab trough level at induction to predict outcome and mucosal healing during maintenance

In the study population, the median VDZ TLs were 34 (IQR: 23–38) μg/ml at week 2, 27 (IQR: 15–38) μg/ml at week 6 and 14 (IQR: 6.7–27) μg/ml at week 14. Without additional infusion at week 10, the median TLs at week 14 were 11.8 (IQR: 3.1–22.2) μg/ml but significantly higher with the additional infusion [mean (IQR): 26.9 (16.7–29.4) μg/ml, $P = 0.001$].

There was no difference in TLs at induction between CD and UC. At week 2, the median TL was 34 (IQR: 23–38) μg/ml for CD patients and 30 (IQR: 22–40) μg/ml for UC patients ($P = 0.98$). At week 6, the median TL was 27 (IQR: 15–38) and 22 (IQR: 14.25–33) μg/ml for CD and UC patients, respectively ($P = 0.35$). At week 14, the median TL was 15.9 (IQR: 4.3–27.4) μg/ml for CD and 14.4 (IQR: 5.7–26) μg/ml for UC ($P = 0.86$).

TLs were not different depending on outcomes at week 2 ($P = 0.926$). In contrast, at week 6, patients experiencing a long-term response had higher TLs than patients in the treatment failure group [33 (IQR: 22–45) vs. 24 (IQR: 14–36l) μg/ml, $P = 0.02$; Fig. 1a). On dividing the TL distribution at week 6 into quartiles (TL Q1 < 17.4 μg/ml, TL Q2 = 17.4–28.6 μg/ml, TL Q3 = 28.6–38.6 μg/ml and TL Q4 > 38.6 μg/ml), a symmetrically opposed distribution was observed between long-term response and the treatment failure group (Fig. 1b). A cut-off TL of 28 μg/ml at week 6 predicted sustained response in the follow-up, with an area under curve of 0.723 (95% CI = 0.567–0.878, $P = 0.017$), corresponding to a sensitivity and specificity of 73 and 64%, respectively. TLs at week 6 were also different according to endoscopic disease activity ($P = 0.009$; Fig. 2). Patients achieving mucosal healing between week 14 and 54 had higher median TL at week 6 at 41.65 (IQR: 32.7–52.3) μg/ml compared with patients with persistent mild [mean (IQR): 26 (18.1–29.7) μg/ml] or severe disease activity [mean (IQR): 20.8 (16.4–28.6) μg/ml].

Although the additional week 10 infusion impacted on TLs, week 14 was not a discriminating time-point for the different outcomes ($P = 0.23$). For patients with secondary response after optimization (optimized group), TLs at induction were not discriminating against other outcomes.

Impact of previous exposure to biologics on early vedolizumab trough level at induction and outcome during maintenance

In univariate analysis, a previous exposure to anti-TNFα was a variable that was associated with VDZ failure in the follow-up, with an OR of 3.6 (95% CI: 1.2–11.2, $P = 0.02$). In patients from the treatment failure group, 83% had been treated previously with at least one anti-TNFα, which was higher than patients from the long-term response group, $P = 0.02$ (Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A393*). Similarly, in univariate analysis, a previous exposure to anti-TNFα was a variable associated with TL less than 28 μg/ml at week 6 with an OR of 6.18 (95% CI: 1.1–34.7, $P = 0.04$).

At week 2, the median TLs were not different, whether the patients had been exposed previously to anti-TNFα or not ($P = 0.69$). At week 6, the median TL was higher in biologic naive patients than in patients exposed previously to anti-TNFα [mean (IQR): 36 (29–42) vs. 22.5 (15–34.5) μg/ml,

Table 1. Demographic and baseline data of the study population

	All patients ($N=81$)	Optimized group ($n=12$)	Long-term responders group ($n=33$)	Treatment failure group ($n=36$)	P value*
Sex [*n* (%)]					
Females	40 (49.4)	7 (58.3)	14 (42.4)	19 (52.7)	0.55
Males	41 (50.6)	5 (41.7)	19 (57.6)	17 (47.3)	
Age (years)	36 (17–89)	27 (21–32)	40 (17–78)	38 (17–89)	**0.002**
Disease features					
Crohn's disease	40 (49.4)	7 (58.3)	10 (30.3)	23 (63.9)	**0.02**
Ulcerative colitis	41 (50.6)	5 (33.3)	23 (57.6)	13 (30.6)	**0.02**
Age at diagnosis					
A1 (< 17 years)	15 (18.5)	4 (57.1)	3 (30)	8 (34,8)	0.5
A2 (17–40 years)	50 (61.7)	3 (42.9)	7 (70)	11 (47.8)	0.5
A3 (>40 years)	14 (17.3)	–	–	2 (8.7)	0.4
Unknown	2 (2.5)	–	–	2 (8.7)	–
Crohn's disease					
Location					
L1	8 (20)	1 (14.3)	3 (30)	4 (17.4)	0.485
L2	6 (15)	2 (28.6)	2 (20)	2 (8.7)	0.382
L3	26 (65)	4 (57.1)	5 (50)	17 (73.9)	0.371
+L4	8 (20)	–	2 (20)	6 (26.1)	–
Behaviour					
B1	12 (30)	3 (42.8)	6 (46)	3 (13.1)	**0.02**
B2	12 (30)	2 (28.6)	3 (16)	7 (30.4)	0.8
B3	16 (40)	2 (28.6)	1 (34)	13 (56.5)	**0.04**
Anoperineal disease	22 (55)	4 (33.3)	3 (9.1)	15 (41.7)	0.17
Ulcerative colitis					
Location					
E1	2 (4.9)	–	2 (8.7)	–	–
E2	20 (48.8)	4 (80)	9 (39.1)	7 (53.8)	0.23
E3	19 (46.3)	1 (20)	12 (52.2)	6 (46.2)	0.41
Smoking status					
Yes	14 (17.3)	1 (8.3)	4 (12.1)	9 (25)	
No	56 (69.1)	9 (75)	25 (75.8)	22 (61.1)	0.55
Previous	11 (13.6)	2 (16.7)	4 (12.1)	5 (13.9)	
Previous biotherapy					
No	22 (27.2)	4 (33.3)	17 (51.5)	9 (25)	0.07
Yes	59 (72.8)	8 (66.6)	16 (48.5)	27 (75)	0.07
Anti-TNF	59	8	16	27	0.07
One	25 (42.4)	2 (25)	8 (50)	4 (14.8)	–
Two	28 (47.5)	4 (50)	7 (43.75)	17 (66.6)	–
Three	6 (10.1)	2 (25)	1 (6.25)	6 (22.2)	–
Vedolizumab	2	–	1	1	–
Anti-P19 antibody	1	–	–	1	–
Concomitant medications at baseline					
None	37 (43.2)	7 (58.3)	15 (45.4)	15 (41.7)	0.07
Steroids	24 (29.6)	2 (16.7)	11 (33.3)	11 (30.6)	0.5
Immunomodulator	28 (34.6)	4 (33.3)	11 (33.3)	13 (36.1)	0.2
Thiopurine	20 (71.4)	1(25)	9 (81.9)	11 (84.6)	–
Methotrexate	8 (28.6)	3 (75)	2 (18.1)	2 (15.4)	–
Follow-up					
Median duration (months)	22 (1–31)	26 (9–31)	11 (3–27)	6 (1–20)	**< 0.0001**
History of surgery	33 (40.7)	6 (50)	8 (24.2)	19 (52.8)	**0.04**

TNF, tumour necrosis factor.
Bold values are statistically significant.
*P value comparing different outcomes.

$P=0.03$; Fig. 3a]. On dividing the TL distribution at week 6 by quartiles (TL Q1 < 17.4 μg/ml, TL Q2 = 17.4–28.6 μg/ml, TL Q3 = 28.6–38.6 μg/ml and TL Q4 > 38.6 μg/ml), there was a higher proportion of patients who had been exposed previously to anti-TNFα in Q1 and Q2 and a higher proportion of naive patients in Q3 and Q4 (Fig. 3b). ATI were measured at the baseline in 40 of 49 patients exposed previously to IFX. ATI were detected in 37.5% of patients. The proportion of ATI detection was similar in the three outcome groups, $P=0.89$. At week 2, patients without detectable ATI had a median TL of 29.3 (IQR: 21.9–37.8) μg/ml and patients with detectable ATI had a median TL of 30.6 (IQR: 23.8–38.4) μg/ml, $P=0.65$. At week 6, patients without detectable ATI had a median TL of 21.1 (IQR: 14.8–31.2) μg/ml and patients with detectable ATI had a median TL of 22 (IQR: 14.4–33.8) μg/ml, $P=0.88$.

Predictive markers associated with vedolizumab trough level at induction and outcome during maintenance

Variables associated with vedolizumab failure

In univariate analysis, a previous treatment with anti-TNFα ($P=0.02$), CD ($P=0.03$) and TL less than 28 μg/ml ($P=0.02$) were predictive variables associated with VDZ failure during maintenance. In multivariate analysis, only TL less than 28 μg/ml was an explanatory variable associated with VDZ failure during maintenance, but only with a trend towards significance ($P=0.054$; Table 2).

Variables associated with vedolizumab trough level less than 28 μg/ml at week 6

In univariate analysis, a previous treatment with anti-TNFα ($P=0.04$), VDZ treatment failure during maintenance

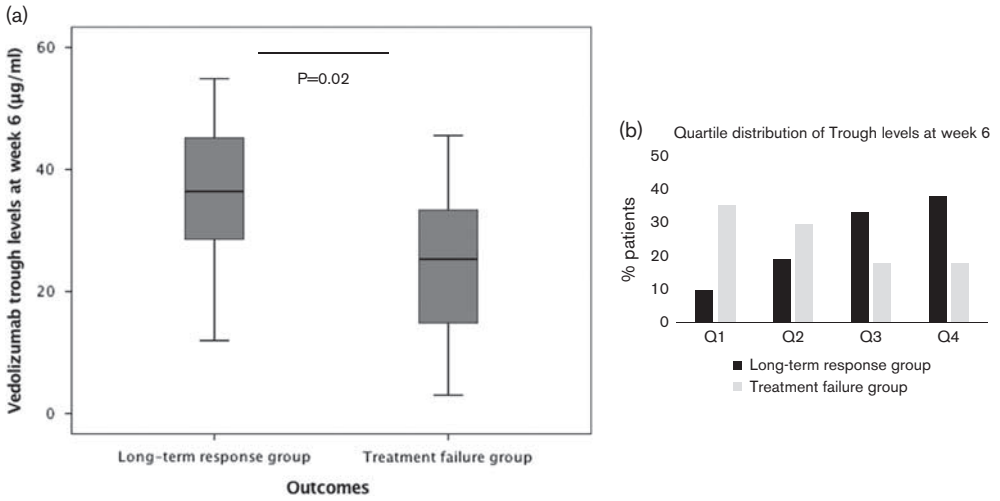

Fig. 1. (a) Median VDZ TL at week 6 between the long-term response and treatment failure groups. The median VDZ TL was 33 (IQR: 22–45) µg/ml in the long-term response group and 24 (IQR: 14–36) µg/ml in the treatment failure group ($P = 0.02$). (b) Quartile distribution of TLs at week 6 according to the outcomes. Q1 < 17.4 µg/ml; Q2 = 17.4–28.6 µg/ml; Q3 = 28.6–38.6 µg/ml; Q4 > 38.6 µg/ml. IQR, interquartile range; TL, trough level; VDZ, vedolizumab.

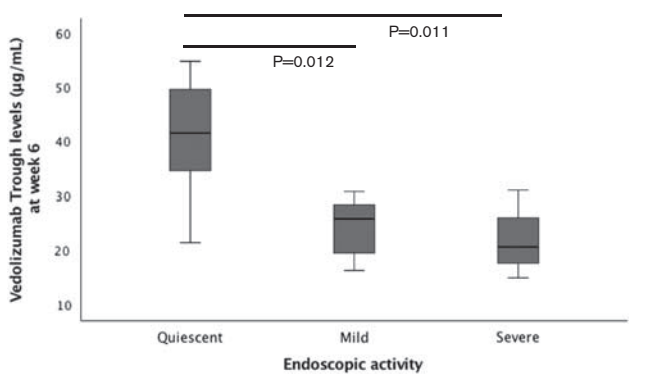

Fig. 2. Median VDZ TLs at week 6 according to endoscopic disease activity between week 14 and 54. Patients with quiescent endoscopic activity (mucosal healing) had a median TL of 41.65 (IQR: 32.7–52.3) µg/ml compared with patients with mild [mean (IQR): 26 (18.1–29.7) µg/ml, $P = 0.012$] or severe disease activity [mean (IQR): 20.8 (16.4–28.6) µg/ml, $P = 0.011$]. IQR, interquartile range; TL, trough level; VDZ, vedolizumab.

($P = 0.02$) and positive ANCA serology ($P = 0.04$) were variables associated with TL less than 28 µg/ml at week 6. In multivariate analysis, only VDZ treatment failure during maintenance was an explanatory variable associated with TL less than 28 µg/ml, but without significance ($P = 0.054$; Table 3). A significant inverse correlation was found between CRP and TLs during induction (Spearman's $\rho = -0579$, $P = 0.002$). However, baseline CRP was not found to be a predictive variable associated with TL less than 28 µg/ml using logistic regression.

Impact of immunomodulator on vedolizumab trough level at induction and outcome during maintenance

When VDZ was initiated, 34.5% of the overall cohort ($n = 28/81$) were treated with an IMM [methotrexate ($n = 8$) and thiopurine ($n = 20$)]. The presence of an IMM at VDZ induction did not influence the outcome during maintenance ($P = 0.75$). The proportion of IMM was similar between groups ($P = 0.2$): 30% in the long-term response group ($n = 10/33$), 42% in the optimized group ($n = 5/12$) and 36% in the failure group ($n = 13/36$) (Supplementary Fig. 2, Supplemental digital content 2, *http://links.lww.com/EJGH/A394*).

The median TLs at induction were not different according to the presence or absence of IMM. At week 2, the median TLs were measured at 29 (24.5–36.5) and 34.5 (27–48) µg/ml with and without an IMM, respectively ($P = 0.9$). At week 6, the median TLs were measured at 24 (17.5–38.5) and 28 (14.3–36) µg/ml with and without an IMM, respectively ($P = 0.9$).

In the subanalysis focusing on the type of IMM, the median TLs were not influenced, irrespective of the IMM, methotrexate or thiopurin. At week 2, the median TLs were measured at 29 (24.5–37) and 30 (24–36) µg/ml with thiopurin and methotrexate, respectively ($P = 0.6$). At week 6, the median TLs were measured at 27 (17.5–38.5) and 22 (16.3–37.5) µg/ml with thiopurin and methotrexate, respectively ($P = 0.6$).

Evolution of vedolizumab trough level during maintenance

By pooling TLs in maintenance (M1–M14), the median VDZ TL in the overall cohort was 10 (IQR: 7–16.75) µg/ml. TLs were less than 1 and less than 3 µg/ml in 9/283 (3.2%) and 26/283 (9.2%) samples, respectively. The median VDZ TLs were similar in the three outcomes: Long-term response group [mean (IQR): 11 (7–16)], the optimized group [mean (IQR): 9.5 (5–15.7) µg/ml] and the treatment failure group [mean (IQR): 9 (5–14) µg/ml] ($P = 0.3$). Similarly, the median VDZ TLs were not different between patients treated with monotherapy or combotherapy [mean (IQR): 10 (7–16) vs. 9 (4.5–17) µg/ml, $P = 0.17$]. By dividing the TL distribution into quartiles, no trend in favour of combotherapy was observed (data not shown).

Discussion

In this study, we have evaluated the pharmacokinetics of VDZ at induction on long-term response. Patients who failed VDZ treatment had significantly lower median TLs at induction than patients with long-term response.

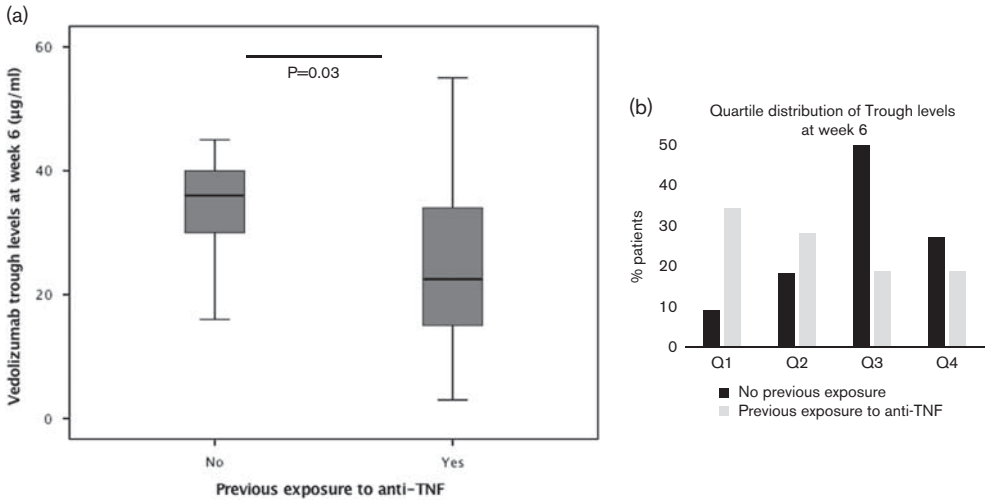

Fig. 3. (a) Median VDZ TL at week 6 in naive or previous exposure to anti-TNFα groups. The median VDZ TL was 22.5 (IQR: 29–42) µg/ml in previously exposed patients and 36 (IQR: 29–42) µg/ml in naive patients ($P = 0.03$). (b) Quartile distribution of TLs at week 6 according to anti-TNFα status. Q1 < 17.4 µg/ml; Q2 = 17.4–28.6 µg/ml; Q3 = 28.6–38.6 µg/ml; Q4 > 38.6 µg/ml. IQR, interquartile range; TL, trough level; TNFα; tumour necrosis factor-α; VDZ, vedolizumab.

Table 2. Variables associated with vedolizumab failure during maintenance

	Univariate analysis			Multivariate analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Sex (female vs. male)	0.72	–	–	–	–	–
Disease type (CD vs. UC)	0.03	3.1	1.15–8.3	–	–	–
Previous anti-TNF (yes vs. no)	0.02	3.68	1.21–11.24	–	–	–
VDZ trough level (cutoff 28 µg/ml) (below vs. above)	0.02	5.16	1.23–21.5	0.054	7	0.96–50.56
Baseline CRP (cutoff 5 mg/l) (below vs. above)	0.23	–	–	–	–	–
Smoking status (yes vs. no)	0.72	–	–	–	–	–
Immunomodulator (yes vs. no)	0.72	–	–	–	–	–
ASCA serology (positive vs. negative)	0.75	–	–	–	–	–
ANA serology (positive vs. negative)	0.79	–	–	–	–	–
pANCA serology (positive vs. negative)	0.79	–	–	–	–	–

ANA, antinuclear antibodies; ASCA anti-*Saccharomyces cerevisiae* antibodies; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; pANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumour necrosis factor; VDZ, vedolizumab.

Table 3. Variables associated with vedolizumab trough level <28 µg/ml at week 6

	Univariate analysis			Multivariate analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Sex (female vs. male)	0.74	–	–	–	–	–
Disease type (CD vs. UC)	0.5	–	–	–	–	–
Previous anti-TNF (yes vs. no)	0.04	6.18	1.1–34.7	–	–	–
VDZ failure (yes vs. no)	0.02	5.16	1.23–21.5	0.054	7	0.96–50.56
Baseline CRP (cutoff 5 mg/l) (below vs. above)	0.68	–	–	–	–	–
Smoking status (yes vs. no)	0.52	–	–	–	–	–
Immunomodulator (yes vs. no)	0.75	–	–	–	–	–
ASCA serology (positive vs. negative)	0.53	–	–	–	–	–
ANA serology (positive vs. negative)	0.75	–	–	–	–	–
pANCA serology (positive vs. negative)	0.04	5.6	1.07–29.37	–	–	–

ANA, antinuclear antibodies; ASCA anti-*Saccharomyces cerevisiae* antibodies; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; pANCA, perinuclear antineutrophil cytoplasmic antibody; TNF, tumour necrosis factor; VDZ, vedolizumab.

This difference was even more pronounced in patients exposed previously to anti-TNFα. Higher TLs at induction were associated with mucosal healing at endoscopy within the first year. VDZ TLs at week 6 appeared to be the most indicative and potentially clinically useful predictive marker of treatment failure. VDZ TLs at induction were not different between patients on VDZ alone or on combotherapy with an IMM.

The small amount of VDZ required to saturate the $\alpha_4\beta_7$ receptor of lymphocytes does not support the drug exposure–efficacy model [19]. This observation questions the use of TDM in the management of patients treated with VDZ. We and others confirmed that VDZ TL at week 6 correlates with clinical outcome [15–17,20]. The TL cutoff of 28 µg/ml at week 6 is higher in this study than the cutoffs reported in other studies [15,17]. ELISA kits are different

between studies, but our proposed threshold is similar to the threshold reported in one study using the same ELISA kit [16]. Also, the proposed cutoffs depend on the outcome such as mucosal healing [15], need for optimization [17] or sustained response such as in this study. Another observation questioning the relevance of VDZ TDM was the absence of a relationship between TL measured during maintenance and outcome as observed previously [17,21]. Although proactive TDM of IFX therapy have not been validated as yet in randomized-controlled trials [22], a positive correlation between IFX TLs in maintenance and outcome has been reported repeatedly [23]. Here, the absence of a drug exposure–efficacy model in maintenance suggests again that the VDZ and IFX pharmacokinetics are dissimilar and that VDZ pharmacokinetics needs to be examined further.

Although our study was designed to evaluate VDZ pharmacokinetics and not clinical response, remission or safety, the proportion of patients who failed VDZ presented in this study is quite high compared with other real-world experiences [9,24–26], even if already described [27]. Our population of CD patients was a refractory population with a high proportion of complicated disease and previous use of two or three anti-TNFα. Also, the median follow-up was 22 months, which was a longer period of follow-up compared with other studies [9,25,26]. Adverse events reported in this study were either well known with VDZ (arthralgia and sinusitis) or specifically related to this significant cohort of patients (testicular neoplasia, CD complication and patient decision). The rate of discontinuation was very similar to other real-world experience cohorts [9,26,27] considering our median follow-up.

Interestingly, we observed that previous exposure to anti-TNFα was associated with lower VDZ TLs at induction and that previous immunogenicity to anti-TNFα, specifically IFX, seems not to influence these low VDZ TLs. The impact of previous exposure to anti-TNFα on clinical remission has already been reported in several studies [20,28]. Patients exposed previously to anti-TNFα often have a more refractory disease course with several negative predictive markers of response such as a long disease duration, extensive disease or a complicated disease. Indeed, patients experiencing a treatment failure had been exposed more frequently to anti-TNFα than patients with long-term response with previous exposure to two or three different anti-TNFα. In addition to this influence of previous exposure to anti-TNFα on clinical outcome, the impact of a previous exposure to anti-TNFα on VDZ pharmacokinetics is less documented. From the population pharmacokinetic model, the clearance of VDZ was significantly faster in patients exposed previously to anti-TNFα compared with those who were anti-TNFα naive, but this difference was considered not to be clinically relevant by the authors [13]. From real-world experience studies, CD patients with recent anti-TNFα exposure had lower trough VDZ levels at all time-points compared with patients with no recent anti-TNFα exposure [29]. Several alternative factors appear to be associated with or influence the pharmacokinetics of VDZ. We examined whether persistent ATI could influence VDZ pharmacokinetics at induction, but our results are not in favour of this hypothesis. Moreover, the great majority of ATI (>90%) is neutralizing antibodies, which specifically bind the same position as where TNF would [30]. A cross-neutralization by targeting a nonspecific region of antibody (such as Fc portion) is not yet excluded. If this mechanism really exists, the impact therefore remains weak and must not be the main driver of these low VDZ TLs in patients with previous exposure to anti-TNFα. These low VDZ TLs could also be related to a high inflammatory burden (high CRP and low albumin). A negative correlation was observed between CRP and VDZ TLs at induction. Positive pANCA serology was also a predictive variable in this study that can easily be measured in clinical practice. pANCA has already been evaluated for its association with responsiveness to anti-TNFα [31–33], but to our knowledge, this is the first time that pANCA was evaluated as a predictive variable associated with VDZ pharmacokinetics.

The use of a concomitant IMM, mainly azathioprine, was reported to be beneficial with IFX treatment by preventing immunogenicity in patients on episodic maintenance [34], by improving clinical response, remission and mucosal healing [35], and by increasing IFX TLs compared with monotherapy [36]. Synergy on efficacy or prevention of immunogenicity may both concur to these positive outcomes. The impact of combotherapy on patients with VDZ has been evaluated in real-world experience cohort studies, but with opposite conclusions [15,21,37,38]. Our study suggested that the use of concomitant IMM did not alter the pharmacokinetics of VDZ either at induction or during maintenance, confirming the results of other studies [15,21].

Our study has a few limitations. First, despite prospective collection of blood samples, the study design remains retrospective, with missing values/data, which could impact the robustness of this study. Second, AVAs were not evaluated. However, VDZ immunogenicity seems to be low according to the initial studies [8,11,19]. These observations were confirmed in real-world studies in which very few patients developed AVAs [17]. This low level of immunogenicity was not exacerbated in anti-TNFα previously exposed populations compared with anti-TNFα-naive patients [28]. When present, AVAs were often transient and infrequently persist in maintenance [21], and therefore modestly impact the pharmacokinetics of VDZ.

Conclusion

A drug exposure–efficacy association exists at induction and could help differentiate patients who will maintain response or fail to VDZ during treatment maintenance. Previous exposure to anti-TNFα and positive pANCA serology were predictive variables associated with VDZ TL less than 28 μg/ml at week 6.

Acknowledgements

The authors thank the Apdia group for their commercial efforts in the purchase of enzyme-linked immunosorbent assay kits.

D.F. received an educational grant by Takeda. C.L. is supported by FNRS (Belgian National Fund of Scientific Research) and D.F. is research director of FNRS.

Conflicts of interest

There are no conflicts of interest.

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