Translating results from VARSITY to real world: adalimumab versus vedolizumab as first-line biological in moderate-to-severe IBD.

Annick Moens[1,2], Bram Verstockt[1,2], Dahham Alsoud[2], João Sabino[1,2], Marc Ferrante[1,2], Séverine Vermeire[1,2].

[1]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

[2]Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium.

Short title: Adalimumab versus vedolizumab as first line biological in moderate-to-severe IBD.

Author contributions:

AM: data acquisition, data analysis and interpretation, statistical analysis, and manuscript writing; DA: data acquisition; BV, JS, MF, SV: study concept and design, data analysis and interpretation, manuscript critical revision.

Conflicts of interest

AM: None

BV reports financial support for research from Pfizer; lecture fees from AbbVie, Biogen, Chiesi, Dr Falk Pharma, Ferring, Galapagos, Janssen, MondayNightIBD, MSD, Pfizer, R-Biopharm, Takeda and Truvion; consultancy fees from Janssen, Guidepont and Sandoz.

DA: None

JS has received speaker's fees from Falk, AbbVie, and Takeda, consultancy fees from Janssen and Fresenius Kabi.

MF has received grants from Amgen, Biogen, Janssen, Pfizer and Takeda; personal Fees from AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Celltrion, Dr. Falk Pharma, Ferring, Janssen, Lamepro, Lilly, Medtronic, MSD, Mylan, Pfizer, Sandoz, Takeda, Thermo Fisher and Truvion Healthcare; and non-financial support from AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Celltrion, Dr. Falk Pharma, Ferring, Janssen, Lamepro, Lilly, Medtronic, MSD, Mylan, Pfizer, Sandoz, Takeda, Thermo Fisher and Truvion Healthcare.

SV has received grants from AbbVie, J&J, Pfizer, and Takeda; and has received consulting and/or speaking fees from AbbVie, Arena Pharmaceuticals, Avaxia, Boehringer-Ingelheim, Celgene, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, Hospira, Janssen, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Takeda, Theravance, and Tillots Pharma AG.

Abbreviations:

ADM: adalimumab; AE: adverse event; CD: Crohn's disease; CI: confidence interval; CRP: C-reactive protein; CS: corticosteroids; GI: gastrointestinal; HBI: Harvey Bradshaw Index; IBD: inflammatory bowel disease; IM: immunomodulator; IQR: interquartile range; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; n: sample size; OR: odds ratio; PGA: physician global assessment; PY: patient years; SAE: serious adverse event; SES-CD: simple endoscopic score for CD patients; SL: serum level; UC: ulcerative colitis; VDZ: vedolizumab; wks: weeks; yrs: years.

Funding

AM is a doctoral fellow and JS, SV, and MF are Senior Clinical Investigators of the Research Foundation Flanders (FWO), Belgium. JS and DA are supported by grants of the Helmsley Charitable Trust.

Short summary: In biological-naïve IBD patients, vedolizumab is superior to adalimumab as first-line agent in ulcerative colitis regarding endoscopic endpoints and treatment persistence, but efficacy of both agents as first-line therapy in Crohn's disease patients was not different.

Correspondence address:

Séverine Vermeire, MD, PhD

Herestraat 49, 3000 Leuven, Belgium

Severine.vermeire@uzleuven.be

Tel: 016/34.42.18 and Fax: 016/34.44.19

Abstract

Background

Selecting a first-line therapy remains challenging in IBD. Adalimumab (ADM) and vedolizumab (VDZ) effectively lead to endoscopic remission in moderate-to-severe IBD. The VARSITY trial showed superiority of VDZ over ADM in ulcerative colitis (UC) regarding clinical remission and endoscopic improvement at week 52. We explored these results in a real-world setting of UC and Crohn's disease (CD).

Methods

Retrospective cohort study of biological-naive patients starting ADM or VDZ between 2015-2019. Patients had moderate-to-severe disease (endoscopic Mayo score ≥ 2 for UC, presence of ulcerations for CD) prior to therapy initiation. For UC, endoscopic remission (endoscopic Mayo score 0) and improvement (endoscopic Mayo score ≤ 1) at week 52 were assessed. For CD, endoscopic remission (absence of ulcerations) and improvement (markedly better endoscopy despite ulcerations) at weeks 26-52 were studied. Treatment persistence was also evaluated.

Results

In total 195 biologic-naive patients (109 UC; 86 CD) were included. In UC, VDZ was superior to ADM regarding endoscopic remission (29% vs 11%, p=0.03) and improvement (51% vs 26%, p=0.01) at week 52 as well as treatment persistence (p=0.04). In CD, no differences in endoscopic remission (VDZ: 48% vs ADM: 60%, p=0.37) and improvement (VDZ: 76% vs ADM: 77%, p=1.00) at weeks 26-52 as well as treatment persistence (p=0.43) was seen. Safety profiles were similar in UC and CD.

Conclusion

This real-world cohort study of biological-naive IBD patients found VDZ to be superior to ADM as first-line treatment for patients with UC, but not CD, regarding endoscopic remission at week 52 and treatment persistence.

Keywords:

Adalimumab – vedolizumab – first-line – ulcerative colitis – Crohn's disease - VARSITY

Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic intestinal inflammation with a typical relapsing and remitting course necessitating long-term medical treatment in the majority of patients.[1] Nowadays, biological therapies including anti-TNFs such as adalimumab (ADM) and anti-integrins such as vedolizumab (VDZ) represent the cornerstone for the management of moderate-to-severe IBD. Both ADM and VDZ are IgG1 monoclonal antibodies that target different pathways contributing to the chronic intestinal inflammation seen in IBD. Whilst ADM blocks tumour necrosis factor, VDZ blocks the interaction between integrin α4β7 on gut-homing T-lymphocytes and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) on gut endothelial cells. Both agents were found to be effective at inducing and maintaining clinical as well as endoscopic remission in patients with moderate-to-severe IBD.[2-8] Thus far, only one head-to-head trial directly comparing both therapies in UC patients has been published. The VARSITY trial concluded that VDZ was superior to ADM in regards to achieving clinical remission and endoscopic improvement after one year.[9] While these results are of clinical importance, some methodological flaws were raised. For instance, patients could not be dose-intensified, and a difference in steroid-free clinical remission could not be demonstrated. Furthermore, not all included patients were biological naive. Last, the trial was conducted in UC and it is unknown if the same conclusion would apply to CD patients.[10] The aim of our study was to explore if the results obtained by VARSITY withstand in a real world setting of UC patients, and if they are also valid for CD patients.

Materials and methods

Study population

This was a retrospective cohort study that included all IBD patients initiating ADM and VDZ treatment at our tertiary referral centre between January 2015 and December 2019. Patients were eligible if the subsequent inclusion criteria were met: at least 18-years old at start of treatment, biological naive, treatment initiation outside clinical trials or medical need programs, indication for treatment being

active moderate-to-severe luminal disease (endoscopic Mayo sub score≥ 2 in UC and presence of ulcerations in CD) as objectified by endoscopic assessment prior to start of therapy, follow-up until at least first endoscopic assessment of treatment independent of treatment continuation [thus at least 8 (ADM) or 14 (VDZ) weeks for UC patients and 26 weeks for CD patients]. Optimization of therapy was allowed if deemed necessary by the treating gastroenterologist and according to the label.

Variables of interest

The following baseline characteristics were extracted from the electronic medical records: gender, IBD diagnosis, age at IBD diagnosis and start of ADM or VDZ, disease duration, smoking status, maximal disease extent according to the Montreal classification,[11] start- and if applicable- stop date of treatment and reason for discontinuation, induction and maintenance regimen as well as need, timing and reason for treatment optimization. The following additional variables were collected at baseline, week 8-14 (UC), week 26 (CD) and week 52: corticosteroids (CS) and immunomodulator (IM) use, C-reactive protein (CRP), faecal calprotectin, partial Mayo score and Harvey Bradshaw Index (HBI). Endoscopic evaluation in UC took place at week 8 (ADM group) and 14 (VDZ group) and week 52 with determination of endoscopic Mayo score. Based on recent literature,[12] first endoscopic evaluation in CD patients after start of biological therapy in our centre shifted from week 26 to 52. Therefore, the first endoscopic evaluation in the CD cohort was assessed at weeks 26-52. At the time of endoscopy, Simple Endoscopic Score for CD patients (SES-CD) was calculated as well as median time to endoscopy.

Definitions

Endoscopic remission in UC and CD were defined as an endoscopic Mayo score of 0 and absence of ulcerations, respectively. Endoscopic improvement was defined as an endoscopic Mayo score ≤1 and markedly better endoscopy, based on physician's assessment, despite still presence of ulcerations in UC and CD patients, respectively.

Clinical remission was defined as a modified Mayo score <2 with rectal bleeding <1 for UC patients and HBI < 5 for CD patients. If clinical scores were not available, physician global assessment (PGA) was used and corresponded to either “remission” or “no remission” based on the clinical judgement of the treating gastroenterologist. For steroid-free endoscopic and clinical remission, the same definitions as endoscopic and clinical remission were used, but with the extra condition that at that moment patients also needed to be off steroids.

Dose intensification or interval shortening compared to standard regimens were regarded as treatment optimization. During the first year of treatment with ADM and VDZ, only reactive optimization in patients with secondary loss of response, with accompanying low drug levels, was performed. Treatment persistence at end of follow-up was defined by patients still being on ADM or VDZ by the end of follow-up, which was December 2020 or last day of follow-up in case of loss to follow-up or discontinuation of treatment.

An adverse event (AE) was defined as any complication occurring during therapy that does not necessarily have a causal relationship with the treatment. A serious adverse event (SAE) was defined as a complication that resulted in death, hospitalization or prolongation of hospitalization, change in IBD treatment or which was life-threatening. Serious infections were those requiring hospitalization or change in IBD treatment.

Standard treatment regimen of ADM consisted of induction with 160mg at week 0 and 80mg at week 2 followed by a maintenance dose of 40mg every other week administered subcutaneously from week 4 onwards. For VDZ, standard therapy consisted of the intravenous administration of 300mg at weeks 0, 2, 6 (and week 10 in case of CD) followed by a maintenance scheme of 300mg every 8 weeks given intravenously from week 14 onwards.

Endpoints

The primary endpoint of this study was endoscopic remission at week 52 (UC) and weeks 26-52 (CD). Secondary endpoints included endoscopic remission and improvement at week 8-14 (UC) and

endoscopic improvement at week 52 (UC) and weeks 26-52 (CD), clinical remission for UC at week 8-14 and 52 and for CD at weeks 26 and 52, corticosteroid-free clinical and endoscopic remission were assessed at the same time points as clinical and endoscopic remission. Treatment persistence was evaluated at the end of follow-up. We also assessed adverse events reported throughout the first year of follow-up.

Ethical consideration

This study was approved by the Institutional Review Board of the University Hospitals Leuven (B322201213950/S53684) in the framework of our VLECC registry. Informed consents were provided by all included patients. Data sharing is not applicable in this research article due to privacy matters and therefore it was not approved by the Institutional Review Board.

Statistical analyses

Efficacy and safety data were analysed according to treatment group for the UC and CD cohort separately. Missing values for binary outcomes were imputed as nonresponses. Categorical variables are presented as frequencies and percentages, whilst continuous variables are shown as medians with interquartile ranges (IQR). For the univariate analyses of categorical variables and unpaired continuous variables, Fisher's exact test or Chi square test and an independent two-group Mann-Whitney U test was used, respectively. To assess the associations between predefined outcomes and different covariates, binary logistic regression analyses was performed using a backward Wald method. Covariates reaching statistical significance ($p<0.05$) in the univariate analyses were eligible for multivariable analyses. Poisson regression model with the natural logarithm of the length of the time periods as offset was used to compare the number of adverse events during and after the first year of treatment. Time-to-event outcomes, such as treatment persistence, were evaluated using Kaplan-Meier survival plots. The results were compared by treatment (ADM or VDZ) using log-rank test. IBM

SPSS Statistics 27.0 software package (Armonk, NY, USA) was used. A two-sided p-value < 0.05 was regarded as statistically significant.

Results

Study population

In total, 109 UC (46 ADM, 63 VDZ) and 86 CD (53 ADM, 33 VDZ) were included. CD patients were significantly younger at diagnosis [26 (21.8-32) years vs. 30 (21-43.5) years, p=0.04], more likely to be active smokers (22% vs. 6%, p=0.002) and treated with ADM (62% vs. 42%, p=0.01) as compared to UC patients. Baseline characteristics are displayed in table 1.

Efficacy

Endoscopic remission

At both week 8-14 and week 52, VDZ was superior to ADM in patients with UC (W8-14: 37% vs. 15%, p=0.02; W52: 29% vs. 11%, p=0.03, figure 1A). In univariate analysis, achieving endoscopic remission at week 52 was only associated with biological type (p=0.03) thus no multivariate analysis was performed. Univariate analysis are shown in supplementary table 1.

Endoscopic outcomes for CD patients were assessed at weeks 26-52 with the median time to endoscopy being similar (p=0.113) in the ADM [27 (24-33) weeks] and VDZ group [29 (27-36) weeks], though seven patients in the ADM group did not undergo further endoscopic evaluation. At weeks 26-52, the remission rates were similar between the VDZ and ADM groups (48% vs. 60%, p=0.37).

In CD patients, univariate analysis revealed that pure ileal disease was associated with achieving endoscopic remission at weeks 26-52 as compared to colonic disease (71% vs. 31%, p=0.007) and ileocolonic disease (71% vs. 46%, p=0.046). Endoscopic remission rates can be found in figure 2A. Univariate analysis are shown in supplementary table 2.

Endoscopic improvement

Similar to endoscopic remission, endoscopic improvement rates at week 8-14 (VDZ: 67% vs. ADM: 39%, p=0.006) as well as at week 52 (VDZ: 51% vs. ADM: 26%, p=0.01) were superior for VDZ compared to ADM in UC patients.

Endoscopic improvement rates for CD patients at weeks 26-52 were similar between the VDZ (76%) and ADM (77%) groups (p=1.00). Endoscopic improvement rates are displayed in figure 1B and 2B for UC and CD patients, respectively.

Clinical remission

Based on partial Mayo score, all ADM-treated UC patients had clinically active disease, but three VDZ-treated UC patients had clinical remission at baseline. The latter patients did have endoscopic disease activity and colonoscopy in these patients was performed because of elevated faecal calprotectin (n=1), abdominal pain (n=1) or unknown reasons (n=1).

Looking at UC patients with active disease prior to start of biological treatment, by week 8-14, more VDZ-treated patients as compared to ADM-treated patients reached clinical remission (VDZ: 53% vs. ADM: 28%; p=0.02), yet at week 52, this differences disappeared (VDZ: 47% vs. ADM: 35%, p=0.24).

In the CD cohort, seven and eight patients in the VDZ and ADM group, respectively, did not have clinically active symptoms of diarrhoea or abdominal pain at baseline. These patients were started on biological treatment due to active endoscopic disease (reason for performing colonoscopy in absence of symptoms were: postoperative evaluation (n=6), symptoms other than pain and diarrhoea such as anaemia, weight loss, elevated faecal calprotectin or CRP, active perianal disease and primary sclerosing cholangitis (n=7).

At both week 26 and 52, similar clinical remission rates were seen between both treatments (week 26: VDZ: 77% vs. ADM: 67%, p=0.43; week 52: VDZ: 65% vs. ADM: 64%, p=1.00). Results are shown in figure 2C.

Steroid use and steroid-free remission

At baseline, 23 UC patients in the ADM group (50%) and 39 in the VDZ group (62%) were on steroids. At week 8-14, 58 and 43 patients in the VDZ and ADM group, respectively, remained on biological with 79% in the VDZ group and 91% of patients in the ADM group being off steroids (p=0.17). At week 52, 43 and 20 patients in the VDZ and ADM group, respectively, remained on biological with 95% in the VDZ group and 100% of patients in the ADM group being off steroids (p=1.00).

In UC, the rates of steroid-free clinical remission were numerically though not significantly better for VDZ at week 8-14 (VDZ: 43% vs. ADM: 26%, p=0.10) and week 52 (VDZ: 45% vs. ADM: 35%, p=0.32). At week 52, more VDZ-treated patients as compared to ADM-treated patients were able to achieve steroid-free endoscopic remission (VDZ: 25% vs. ADM: 11%; p=0.08), yet not statistically significant.

For CD patients, 16 in the VDZ group (48%) and 25 patients in the ADM (47%) were on steroids at baseline. At week 26, 32 in the VDZ and 47 patients in the ADM group were still on biological therapy, of which 81% and 96% were able to discontinue steroids in the ADM and VDZ group (p=0.06), respectively. At week 52, 27 and 43 patients in the VDZ and ADM group, respectively, remained on biological with 96% and 98% in the VDZ and ADM group, respectively, being off steroids (p=1.00).

For CD patients with clinically active disease at start of biological therapy, no differences in the rates of steroid-free clinical remission were seen between both groups at week 26 (VDZ: 65% vs. ADM: 67%, p=1.00) and week 52 (VDZ: 65% vs. ADM: 64%, p=1.00) nor for steroid-free endoscopic remission at weeks 26-52, (VDZ: 45% vs. ADM: 67%, p=0.07). Results are shown in figure 1D and 2C.

Rate of surgery

Three ADM-treated (7%) and four VDZ-treated (6%) UC patients needed to undergo a total colectomy after treatment failure (p=1.00). All but one VDZ-treated UC patient first received rescue high dose infliximab before proceeding to surgery.

In the CD cohort, only one ADM-treated patient needed an ileocaecal resection after treatment failure (p=1.00).

Treatment optimization

In total, 37 UC patients underwent treatment optimization. Significantly more patients in the ADM group (n=23, 50%) as compared to the VDZ group (n=14, 22%) underwent treatment optimization within the first year of therapy (p=0.004). The endoscopic remission rates at week 52 in dose-escalated patients did however not significantly differ between both groups (ADM: 4% vs VDZ: 0%, p=1.00).

Twenty-two patients in the CD cohort received treatment optimization. In contrast to UC patients, treatment optimization rates were similar between the ADM (n=16, 30%) and VDZ group (n=6, 18%; p=0.31). Although numerically more ADM-treated CD patients underwent treatment optimization within the first year of therapy as compared to VDZ-treated CD patients, the rates of endoscopic remission in these optimized patients was not significantly different (ADM: 13% vs VDZ: 0%, p=1.00).

When comparing VDZ-treated UC and CD patients, the number of patients undergoing treatment optimization was similar in both cohorts (22% vs. 18%, P=0.79), though a trend towards higher need for treatment optimization was seen in ADM-treated CD patients as compared to UC patients (50% vs. 30%, p=0.06).

Treatment persistence

UC patients were treated with VDZ for a median (IQR) of 66 (22-135) weeks as compared to 33 (10-105) weeks for ADM, (p=0.06). Treatment persistence by the end of follow-up was significantly different between ADM and VDZ in UC patients (p=0.04) and can be seen in figure 3A.

The time on ADM and VDZ for CD patients was 112 (62-206) weeks and 140 (62-191) weeks, respectively (p=0.69). In contrast to UC patients, there was no difference in treatment persistence between ADM and VDZ in CD (p=0.43) as displayed in figure 3B. Reasons for treatment discontinuation can be found in supplementary table 3.

Safety

A total of 24 adverse events were reported in 17 ADM-treated UC patients within the first year of treatment. In the VDZ-treated UC group, 32 adverse events occurred in 20 patients within the first year of therapy. This corresponds to an adverse events rate of 1.96 and 1.97 AE per patient year (PY) of follow-up in the ADM and VDZ group, respectively. One 83-year-old VDZ-treated UC patients, with underlying cardiovascular comorbidity, died before W52 due to acute pulmonary oedema.

For CD patients, 27 patients in the ADM group and 20 in the VDZ group experienced 39 and 32 adverse events, respectively, within the first 52 weeks of treatment. The rate of adverse events for ADM-treated and VDZ-treated patients was 1.76 and 1.73 per PY before week 52, respectively. No deaths occurred in the CD cohort, yet one patient with concomitant primary sclerosing cholangitis received a liver transplant. Detailed description of the various adverse events and serious adverse events can be found in supplementary table 4-6. The number of serious and non-serious adverse did not differ between both treatment groups in UC as well as CD patients. (Supplementary table 7-8, Figure 4).

Discussion

This is the first real-life cohort where efficacy and safety of vedolizumab and adalimumab as first-line treatment for UC and CD were directly compared.

In the UC cohort, we confirmed the results of the VARSITY trial that VDZ was superior to ADM in achieving endoscopic improvement and remission. The superiority of VDZ was also suggested in recently published network meta-analyses, although no difference was seen between VDZ and IFX regarding maintenance of clinical remission and endoscopic improvement.[13, 14] In addition, the Victory consortium investigated the real-life effectiveness of VDZ, but in contrast to our study, the consortium compared their results to results of historic cohorts of anti-TNF treated CD patients. This may explain the differences in results between our CD cohort and results found in the CD cohort of the Victory consortium. Other reasons that might explain these differences are that the patients in the Victory

consortium were not all biological-naive and did not need to have moderate-to-severe active disease based on endoscopic assessment, but clinical assessment was also accepted.

The rates of endoscopic remission for VDZ are similar to those reported in the GEMINI 1 trial, yet the endoscopic remission rate for ADM was lower compared to results from the ULTRA-2 trial.[5, 15, 16] The latter might be due to the real-life nature of this cohort as well as the fact that endoscopic remission rates in this study were assessed separate of clinical response rates. Patients in the Varsity trial could not be dose adjusted, although this is a common real-life practice. In our cohort, we found that patients in the ADM group more frequently underwent optimization as compared to patients in the VDZ group, which is in line with was has been reported in other studies.[17, 18] However, dose optimization did not lead to significantly better endoscopic remission rates in both UC and CD patients. This finding may seem contradictory since dose intensification can lead to improved outcome by overcoming secondary loss of response.[19, 20] However, our results are in line with the more recent data from the SERENE trials in IBD. These suggest that using very high induction doses of ADM do not lead to better clinical nor endoscopic outcomes.[21-24] Another explanation for this contradictory result may be that only patients not responding to therapy and thus who were prone to have a bad outcome, were optimized. It is possible that these patients possess certain characteristics making them inherently refractory to either VDZ or ADM despite the use of more drug. We showed that VDZ is superior to ADM regarding clinical remission at week 8-14, however we were not able to show this at week 52. This may be due to several reasons such as loss to follow-up, patients stopping treatment before week 52, missing and/or incomplete clinical scores so that clinical remission could not be established.

Considering steroid use, similar proportions of patients in both the ADM and VDZ group were able to discontinue steroids by week 8-14 as well as week 52. Furthermore, no differences in rates of steroid-free clinical remission were shown between both treatment groups. However, numerically more VDZ-treated patients were able to achieve steroid-free endoscopic remission at week 52 as compared to ADM-treated UC patients, yet not statistically signifcant. No good explanation exists for these discordant results, since in UC active endoscopic disease was found to be well correlated to clinically

active disease. Steroid-free remission remains an important endpoint in modern era since long-term use of steroids should be avoided given their long-term side effects. If patients cannot taper or stop steroids, we therefore recommend to switch or escalate treatment. Not only did we not find a difference in steroid-free remission, the surgery rate was low in all treatment groups and did not differ between groups. Almost all UC patients that needed to undergo total proctocolectomy after failure of ADM or VDZ still received high dose rescue infliximab without success. In addition, only one ADM-treated CD patient needed an ileocaecal resection three months after start of ADM, suggesting that ADM might have been started too late to reverse the stricturing phenotype of the patient.

Not only did we confirm that VDZ is superior to ADM as first-line therapy in UC patients regarding endoscopic remission, this is also the first real-life study to report superiority of VDZ over ADM regarding treatment persistence. Former trials did not investigate treatment persistence[9], or could not find a significant difference between both treatments[17] or only compared VDZ and anti-TNF therapy as second-line agents.[18]

In contrast to the UC cohort, no differences in outcomes were observed between VDZ and ADM in CD patients. It should be noticed that more ADM-treated CD patients had a stricturing phenotype, whilst more VDZ-treated CD patients had an inflammatory phenotype, although this did not affect endoscopic outcomes. These results are consistent with results shown in prior studies[19, 20] where in CD patients, both anti-integrin and anti-TNF therapy appear to be valid options as first-line treatment. Furthermore, with anti-TNF biosimilars entering the market, they also represents an economically justified option. No head-to-head trials are available, but similar results were reported in a previously published network meta-analysis,[21] though a superiority of infliximab may exist for induction of clinical remission.[22]

Recently, results from the first head-to-head trial in CD patients was made public in which the efficacy of ADM and ustekinumab were compared as first-line agents (SEAVUE). The primary endpoint (superiority of ustekinumab over adalimumab in achieving clinical remission) was not achieved, and in

both treatment arms patients were as likely to achieve clinical as well as endoscopic remission at week 52.[23]

Interestingly, CD patients continued significantly longer on biological therapy as compared to UC patients. This may be explained by the often less pronounced and more vague symptoms found in CD patients as compared to the more objectifiable symptoms (e.g. diarrhoea, blood loss) found in UC patients. However, this might also be related to differences in reimbursement criteria in our country between UC and CD patients. For instance, if no response is seen within 3 months after start of biological therapy in UC patients, treatment needs to be stopped.

Since VDZ is considered to be gut-focused, one may presume that it might have a better overall safety profile compared to ADM, but that there might be a higher risk for gastro-intestinal infections.[19] The latter is reflected in the three *Clostridium difficile* infections that were reported only in VDZ-treated UC patients. In general, the number of reported adverse events per patient was low and comparable between treatment groups. Long term follow up safety data from the registration trials also did not show a difference in adverse events between ADM and VDZ in CD patients, though a more favourable safety profile of VDZ in UC patients has been described.[17, 19, 24, 25]

Our study has some limitations. First, the retrospective nature of this study makes it prone to selection bias, although we diminished this risk by including all patients that met the well-defined inclusion criteria. Second, the relatively small number of patients included in this cohort might explain why some differences in outcome established in the VARSITY trial could not be confirmed here. Third, there were missing clinical scores as well as endoscopic evaluations at the pre-set time points. Finally, the study mainly focusses on the short-term outcome, though treatment persistence was reported for the entire follow-up time.

Conclusion

In this real-world cohort study of biological-naive moderate-to-severe IBD patients, VDZ was superior to ADM as first-line treatment of UC patients with regard to endoscopic remission at week 52 and treatment persistence. In CD patients, no differences were seen between VDZ and ADM as first-line treatment with regard to endoscopic outcomes and treatment persistence. No differences in safety profile were seen between both biological agents in UC and CD patients.

References

1. Johnston RD, Logan RF. What is the peak age for onset of IBD? Inflamm Bowel Dis. 2008;14 Suppl 2:S4-5.
2. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology. 2006;130(2):323-33; quiz 591.
3. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56(9):1232-9.
4. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142(5):1102-11.e2.
5. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257-65.e1-3.
6. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.
7. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-21.
8. Noman M, Ferrante M, Bisschops R, De Hertogh G, Van den Broeck K, Rans K, et al. Vedolizumab Induces Long-term Mucosal Healing in Patients With Crohn's Disease and Ulcerative Colitis. J Crohns Colitis. 2017;11(9):1085-9.
9. Sands BE, Peyrin-Biroulet L, Loftus EV, Danese S, Colombel JF, Törüner M, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019;381(13):1215-26.
10. O'Connor DB, Lahiff C. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2020;382(1):92-3.
11. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005;19 Suppl A:5A-36A.
12. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-83.
13. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(10):2179-91.e6.
14. Jairath V, Chan K, Lasch K, Keeping S, Agboton C, Blake A, et al. Integrating efficacy and safety of vedolizumab compared with other advanced therapies to assess net clinical benefit of ulcerative colitis treatments: a network meta-analysis. Expert Rev Gastroenterol Hepatol. 2021:1-12.
15. Sandborn WJ, Colombel JF, D'Haens G, Van Assche G, Wolf D, Kron M, et al. One-year maintenance outcomes among patients with moderately-to-severely active ulcerative colitis who responded to induction therapy with adalimumab: subgroup analyses from ULTRA 2. Aliment Pharmacol Ther. 2013;37(2):204-13.
16. Sandborn WJ, Colombel JF, Panaccione R, Dulai PS, Rosario M, Cao C, et al. Deep Remission With Vedolizumab in Patients With Moderately to Severely Active Ulcerative Colitis: A GEMINI 1 post hoc Analysis. J Crohns Colitis. 2019;13(2):172-81.
17. Van de Vondel S, Baert F, Reenaers C, Vanden Branden S, Amininejad L, Dewint P, et al. Incidence and Predictors of Success of Adalimumab Dose Escalation and De-escalation in Ulcerative Colitis: a Real-World Belgian Cohort Study. Inflamm Bowel Dis. 2018;24(5):1099-105.

18. Schreiber S, Dignass A, Peyrin-Biroulet L, Hather G, Demuth D, Mosli M, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. J Gastroenterol. 2018;53(9):1048-64.
19. Dalal SR, Cohen RD. What to Do When Biologic Agents Are Not Working in Inflammatory Bowel Disease Patients. Gastroenterol Hepatol (N Y). 2015;11(10):657-65.
20. Peyrin-Biroulet L, Danese S, Argollo M, Pouillon L, Peppas S, Gonzalez-Lorenzo M, et al. Loss of Response to Vedolizumab and Ability of Dose Intensification to Restore Response in Patients With Crohn's Disease or Ulcerative Colitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17(5):838-46.e2.
21. Colombel J.F, Panés J., D'Haens G., Schreiber S., Panaccione R., et al. OP01- Higher vs. standard adalimumab maintenance regimens in patients with moderately to severely active ulcerative colitis: Results from the SERENE-UC maintenance study. European Crohn's and Colitis Organization 2020.

22. D'Haens G. SWJ, Loftus E., Hanauer S.B., Schreiber S., et al. LB27- High versus standard adalimumab induction dosing regimens in patients with moderately to severely active Crohn's disease: results from the Serene-CD induction study. United European Gastroenterology2019.
23. Danese S. SWJ, Loftus E.V., Hanauer S., Schreiber S, et al. Clinically Adjusted vs Therapeutic Drug Monitoring Dosing Regimens With Adalimumab in Patients With Moderately to Severely Active Crohn's Disease: Results From the SERENE-CDMaintenance Study. Digestive Disease Week 2020.

24. Panés J. CJ-F, D'Haens G.R., Schreiber S., Panaccione R., et al. OP216- High versus standard adalimumab induction dosing regimens in patients with moderately to severely active ulcerative colitis: results from the Serene-UC induction study. United European Gastroenterology2019.
25. Bressler B, Yarur A, Silverberg MS, Bassel M, Bellaguarda E, Fourment C, et al. Vedolizumab and Anti-TNFα Real-World Outcomes in Biologic-Naïve Inflammatory Bowel Disease Patients: Results from the EVOLVE Study. J Crohns Colitis. 2021.
26. Helwig U, Braegger F, Kostev K, Schmidt C. Comparative Analysis of the 3-Year Persistence Rate with Second-Line Vedolizumab and Tumor Necrosis Factor-α Inhibitors in Patients with Inflammatory Bowel Disease Followed in Gastroenterology Practices in Germany. Dig Dis. 2020;38(6):466-73.
27. Bohm M, Xu R, Zhang Y, Varma S, Fischer M, Kochhar G, et al. Comparative safety and effectiveness of vedolizumab to tumour necrosis factor antagonist therapy for Crohn's disease. Aliment Pharmacol Ther. 2020;52(4):669-81.
28. Macaluso FS, Ventimiglia M, Fries W, Viola A, Sitibondo A, Cappello M, et al. A propensity score weighted comparison of vedolizumab and adalimumab in Crohn's disease. J Gastroenterol Hepatol. 2021;36(1):105-11.
29. Miligkos M, Papamichael K, Vande Casteele N, Mantzaris GJ, Gils A, Levesque BG, et al. Efficacy and Safety Profile of Anti-tumor Necrosis Factor-α Versus Anti-integrin Agents for the Treatment of Crohn's Disease: A Network Meta-analysis of Indirect Comparisons. Clin Ther. 2016;38(6):1342-58.e6.
30. Singh S, Heien HC, Sangaralingham LR, Schilz SR, Kappelman MD, Shah ND, et al. Comparative Effectiveness and Safety of Anti-Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2016;14(8):1120-9.e6.
31. Sands BE, Hoops T, Izanec JL, Gao L, Gasink C, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in moderate-to-severe Crohn's disease: the Seavue study. Digestive Disease Week 2021.
32. Adar T, Faleck D, Sasidharan S, Cushing K, Borren NZ, Nalagatla N, et al. Comparative safety and effectiveness of tumor necrosis factor α antagonists and vedolizumab in elderly IBD patients: a multicentre study. Aliment Pharmacol Ther. 2019;49(7):873-9.

33. Singh S, Heien HC, Herrin J, Dulai PS, Sangaralingham L, Shah ND, et al. Comparative Risk of Serious Infections with Tumor Necrosis Factor-α Antagonists vs. Vedolizumab in Patients with Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2021.

Table 1: Baseline characteristics (n=195)

	UC (n=109)		CD (n=86)		P-value UC (ADM vs. VDZ)	P-value CD (ADM vs. VDZ)
	ADM (n=46)	VDZ (n=63)	ADM (n=53)	VDZ (n=33)		
Median (IQR) age at start biological (yrs.)	36 (27.5-47.5)	41 (28-56)	31 (24-46.5)	43 (27-56.5)	0.19	**0.04**
Median (IQR) age at diagnosis (yrs.)	26.5 (19.8-44.3)	34 (23-43)	25 (21-30.5)	30 (22-40.5)	0.15	**0.04**
Male sex (%)	22 (48)	25 (40)	25 (47)	17 (52)	0.44	0.83
Current smoker (%)	3 (7)	4 (6)	12 (23)	7 (21)	1.00	1.00
Median (IQR) disease duration (yrs.)	3.5 (1-7.5)	5 (1-11)	3 (0-17)	4 (1-11)	0.76	0.29
Concomitant therapy (%)						
- **Immunomodulator**	7 (15)	4 (6)	6 (11)	2 (6)	0.20	0.71
- **Systemic steroids**	6 (13)	12 (19)	9 (17)	7 (21)	0.45	0.78
- **Topical steroids**	17 (37)	27 (43)	16 (30)	9 (27)	0.56	0.81
Maximum disease extent UC (%)						
- **Proctitis**	5 (11)	14 (22)			0.14	
- **Left-sided colitis**	26 (57)	28 (44)	NA	NA	0.25	NA
- **Extensive colitis**	15 (33)	21 (33)			1.00	
Maximum disease location CD (%)						
- **Ileal disease**			29 (55)	13 (39)		0.19
- **Colonic disease**	NA	NA	8 (15)	8 (24)	NA	0.39
- **Ileocolonic disease**			16 (30)	12 (36)		0.64
Maximum disease behaviour CD (%)						
- **Inflammatory**	NA	NA	26 (49)	21 (64)	NA	0.27
- **Stricturing**			16 (30)	7 (21)		0.46
- **Penetrating**			11 (21)	5 (15)		0.58
Perianal disease CD (%)	NA	NA	11 (21)	2 (6)	NA	0.11
Upper GI disease CD (%)	NA	NA	2 (4)	1 (3)	NA	1.00

CD: Crohn's disease; GI: gastro-intestinal; IQR: interquartile range; NA: not applicable; UC: ulcerative colitis; yrs: years.

Figure legends

Figure 1: Clinical and endoscopic outcomes in patients with UC. Figure 1A shows endoscopic remission; 1B shows endoscopic improvement; 1C displays clinical remission and 1D steroid-free clinical remission at weeks 8 or 14 and 52.

Figure 2: Clinical and endoscopic outcomes in patients with CD. Figure 2A shows endoscopic remission; 2B shows endoscopic improvement; 2C displays clinical remission and 2D steroid-free clinical remission at weeks 26 and 52.

Figure 3: Treatment persistence during follow-up. Orange curve are VDZ and blue curve are ADM-treated patients. Figure 3A shows Kaplan-Meier survival plot of treatment persistence in UC patients. Figure 3B shows Kaplan-Meier survival plot of treatment persistence in CD patients.

Figure 4: Incidence rates of adverse events per patient year of follow-up. CD: Crohn's disease; UC: ulcerative colitis.