Digestive and Liver Disease xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Original Article

The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel diseases

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ARTICLE INFO

Article history:
Received 25 September 2017
Accepted 21 February 2018
Available online xxx

Keywords:
Biologics
Extra-intestinal manifestations
Real-world

ABSTRACT

Background: The effectiveness of vedolizumab in real-world practice is under evaluation, while its role in inflammatory bowel disease-associated spondyloarthritis is still unclear.
Aims: To report real-world data about the effectiveness of vedolizumab on intestinal and articular symptoms after 10 and 22 weeks of treatment.
Methods: Web-based data from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) were extracted to perform a prospective multicentre observational study.
Results: 163 patients (84 with Crohn's disease and 79 with ulcerative colitis) were included. At week 10, a steroid-free remission was achieved in 71 patients (43.6%), while at week 22 a steroid-free remission was obtained in 40.8% of patients. A response on articular symptoms was reported after 10 weeks of treatment in 17 out of 43 (39.5%) patients with active spondyloarthritis at baseline, and in 10 out of 22 (45.4%) patients at week 22. The only factor associated with articular response was the coexistence of clinical benefit on intestinal symptoms (at week 10: OR 8.471, $p = 0.05$; at week 22: OR 5.600, $p = 0.08$).
Conclusions: Vedolizumab showed good effectiveness after 10 and 22 weeks of treatment. A subset of patients reported improvement also on articular symptoms, probably as a consequence of the concomitant control of gut inflammation.

1. Introduction

Intravenously administered, vedolizumab (VDZ) is a new biologic agent approved for the treatment of adult patients with moderately to severely active Crohn's disease (CD) or ulcerative colitis (UC) who had an inadequate response with, lost response to, or were intolerant to either conventional therapy or TNFα inhibitors [1]. The efficacy of VDZ in CD and UC has been demonstrated against placebo in three pivotal phase III randomized controlled trials – GEMINI 1 [2], GEMINI 2 [3] and GEMINI 3 [4]. A fourth open-label, long-term randomized controlled trial – GEMINI LTS – confirmed efficacy of the drug for up to 152 weeks of cumulative treatment in both CD [5] and UC [6]. Recently, endoscopic and histological healing was also observed in a significant proportion of inflammatory bowel disease (IBD) patients treated with VDZ long-term [7]. Furthermore, cumulative data from randomized controlled trials showed that VDZ had a favourable safety profile over an extended treatment period [8]. However, as results derived from randomized controlled trials may differ from the true effectiveness of a drug in clinical settings, real-world studies are needed to confirm the clinical benefit of VDZ. So far, this has been evaluated by some cohorts [9–18], with variable sample sizes and lengths of follow-up. In addition, in case of active IBD-associated spondy-

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https://doi.org/10.1016/j.dld.2018.02.013
1590-8658/

loarthritis (SpA) – a common problem in clinical practice [19] – the effects of VDZ on articular manifestations are still unclear. Indeed, arthralgia, back pain and pain in the extremities were reported as common (≥1/100) or very common (≥1/10) in clinical trials, but no mention of proven arthritis or sacroiliitis was made, probably because this aspect was insufficiently investigated. Similarly, such clinical outcomes were not specifically assessed by real-world cohorts. Recently, Varkas and colleagues [20] reported a series of five patients with IBD who were treated with VDZ and developed new onset or exacerbation of SpA, irrespective of the response on intestinal symptoms, while a preliminary experience showed a sharp reduction or resolution of articular symptoms in a subgroup of patients after the initiation of the drug, thus suggesting a potential benefit of VDZ on IBD-associated SpA [21].

On these premises, web-based data from the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD) were extracted to perform a multicentre, real-world observational study on the effectiveness of VDZ on intestinal and articular symptoms after 10 and 22 weeks of treatment, and to identify the predictors of clinical benefit.

2. Materials and methods

2.1. Patients

The SN-IBD is a group composed by all centres prescribing biologics in Sicily. Since January 2013, these centres continuously enter in a web based software all real-life prospective data on patients with IBD treated with biologics, with the aim of monitoring efficacy, safety, appropriateness, and costs of these therapeutics in Sicily. So, all consecutive patients treated with VDZ from July 2016 (the date on which the drug became available for clinical practice in Sicily) to April 2017 were extracted from the cohort of SN-IBD for the purposes of this study. VDZ was used in adult patients with moderately to severely active UC or CD who had an inadequate response with, lost response to, or were intolerant to either conventional therapy or TNFα inhibitors. The recommended dosage of 300 mg infused intravenously over approximately 30 min at zero, two and six weeks, then every eight weeks thereafter was used, with the possibility of a fourth induction dose in patients with CD and insufficient response to the first three doses, and of a treatment optimization – shortening the administration intervals to every four weeks – in case of inadequate clinical response. Subjects with less than a 10-weeks period of follow-up were excluded from the analysis.

2.2. Data collection and measures of outcome

The following data were collected for each patient at baseline, i.e. at the initiation of VDZ treatment: demographics, smoking status, type of disease (CD vs. UC), duration of the disease, disease extent for UC, disease localization and behaviour, previous small bowel resections, and perianal involvement for CD, disease activity (expressed as Harvey–Bradshaw Index for CD, as Partial Mayo Score for UC, and with C-reactive protein serum values for both diseases), endoscopic activity evaluated within six months before the initiation of VDZ (expressed as Simple Endoscopic Score for CD, Rutgeerts score in patients with CD and previous resections, and Mayo Endoscopic Score for UC), presence of extra-intestinal manifestations – with a detailed focus on history or active peripheral and/or axial SpA evaluated with the Assessment of Spondyloarthritis international Society (ASAS) classification criteria [22,23] – previous use of anti-TNFα therapy (distinguishing between previously exposed vs never exposed), indications to VDZ treatment (distinguishing between previous failure vs. contraindications to anti-TNFα therapy), presence of steroid-dependence, dose of systemic prednisone at baseline, and concurrent therapy with immunosuppressants. All patients were strictly followed to perform an accurate clinical evaluation and a prompt record of all adverse events. The following clinical end points were set at week 10 and 22: steroid-free remission (Harvey–Bradshaw Index < 5 for CD and Mayo Partial Score < 2 for UC without steroids use), and response (absence of steroid-free remission, but reduction of Harvey–Bradshaw Index ≥ 3 for CD and Mayo Partial Score ≥ 2 for UC compared with baseline, with a concomitant reduction of steroid dosage at week 10, and discontinuation at week 22). Patients with steroid-free remission and response were deemed as having clinical benefit, whereas treatment failure was defined as discontinuation of VDZ due to adverse events or clinical inefficacy, i.e. need for surgery, inability to reduce/discontinue steroids, any need for steroids use after their withdrawal or any need for a new increase after their reduction. In patients with active SpA at baseline, the same temporal end points (week 10 and 22) were set to evaluate the response on articular symptoms, defined as disappearance of objective signs of arthritis (swelling and/or articular stiffness) and resolution of pain. New onset or exacerbations of arthritis and/or sacroiliitis in VDZ-treated patients were reported as adverse events ("flare").

2.3. Statistics

Continuous variables were summarized as mean ± standard deviation and categorical variables as frequency and percentage. Mann–Whitney *U*-test and χ^2 test (or Fisher's exact test, where appropriate) were used for the comparison of continuous and categorical variables, respectively. Multiple logistic regression analysis was performed to identify independent predictors of clinical benefit on intestinal manifestations and articular response at week 10 and week 22. Variables associated with the dependent variable on univariate analysis (probability threshold: $p \leq 0.10$) were included in the logistic regression model, then selected using a backward elimination approach; results were considered statistically significant when $p \leq 0.05$.

All statistical analysis was performed using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients at baseline

During the study period, 163 patients (84 with CD and 79 with UC) were included (Table 1). The majority of them (88.3%) were steroid-dependent, and approximately 3 out of 4 had a history of previous exposure to TNF-α inhibitors. Disease activity was expressed by mean values of Harvey–Bradshaw index (8.3 ± 4.6), Partial Mayo score (3.9 ± 2.4), and C-Reactive Protein (9.8 ± 15.7 mg/L; normal values <5 mg/L). Notably, 43 patients (26.4%) had active SpA at initiation of VDZ.

3.2. Clinical effectiveness

After 10 weeks, a steroid-free remission was obtained in 71 patients (overall: 43.6%; CD: 41.7%, UC: 45.6%), while a clinical response in 37 (overall: 22.7%; CD: 22.6%, UC: 22.8%). Among patients who obtained a clinical benefit at week 10, mean C-reactive protein value was 6.4 ± 10.9 mg/L. Out of 71 patients reaching 22 weeks of follow-up, 29 were in steroid-free remission (overall: 40.8%; CD: 41.7%, UC: 40.0%), and 10 had a response (overall: 14.1%; CD: 13.9%, UC: 14.3%). Among patients who obtained a clinical benefit at week 22, mean C-reactive protein value was 4.7 ± 8.3 mg/L. No significant difference in terms of clinical benefit (rate of remission plus response) among patients with CD and UC was reported at week 10 (64.3% vs. 68.4%, respectively; $p = 0.58$) and at week

Please cite this article in press as: Macaluso FS, et al. The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel diseases. Dig Liver Dis (2018), https://doi.org/10.1016/j.dld.2018.02.013