Digestive and Liver Disease xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

Position Paper

Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease

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ARTICLE INFO

Article history:
Received 4 August 2015
Accepted 28 December 2015
Available online xxx

Keywords:
Crohn's Disease
Inflammatory Bowel Disease
Ulcerative Colitis
Vedolizumab

ABSTRACT

Crohn's Disease (CD) and Ulcerative Colitis (UC) are chronic, relapsing conditions resulting from uncontrolled inflammation of the intestinal mucosa. Both conditions are associated with significant disability and patients with CD face higher mortality rates compared to the general population. The increasing understanding of the immunological basis of the disease led to the introduction of biologic therapies targeting key pathways of the natural and adaptive immune response such as Tumor Necrosis Factor α (TNF-α) inhibitors and, more recently, integrin-receptor antagonists. Treatment with TNF-α inhibitors improved clinical and patient-reported outcomes for many patients who did not benefit from conventional therapy. However, a sizeable share of patients still face suboptimal outcomes due to primary or secondary therapy failure. With the introduction of VDZ, a biologic treatment targeting novel IBD-relevant biologic pathways, it is crucial to understand how to integrate such innovations into current clinical practice. To this end, a panel of 14 Italian experts in the management of IBD met for a roundtable discussion. Recommendations concerning the management of moderate-to-severe IBD based on experts' opinions and literature review are discussed in the present report.

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1. Introduction

Crohn's Disease (CD) and Ulcerative Colitis (UC) are chronic, relapsing conditions resulting from uncontrolled inflammation of the intestinal mucosa. Both conditions are associated with significant disability and patients with CD face higher mortality rates compared to the general population [1–3].

The epidemiology of UC and CD has fluctuated in the past 50 years and it is geographically heterogeneous. The population-based prevalence in Italy is $187/10^5$ whereas the yearly incidence of UC, CD and Inflammatory Bowel Disease (IBD) unclassified is $6/10^5$, $5/10^5$ and $1/10^5$ respectively [4]. Prevalence rates extrapolated from hospital discharge claims data were $177/10^5$ and $91/10^5$ for UC and CD, respectively [5]. In the same study, incidence rates were as high as $14.5/10^5$ and $7.4/10^5$ for UC and CD, respectively [5]. However, administrative data used for both the aforementioned studies are prone to information bias and the real burden of IBD may be underestimated with such methods.

Despite the etiology and pathogenesis of IBD remain partially unknown, there has been a dramatic shift in the understanding of such conditions in the past decade. Current research strongly suggests that IBD results from inappropriate and sustained inflammatory reactions initiated by a defective immune response to commensal bacteria residing in the gastrointestinal tract [6].

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http://dx.doi.org/10.1016/j.dld.2015.12.016
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Please cite this article in press as: Armuzzi A, et al. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2015.12.016
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The increasing understanding of the immunological basis of the disease, led to the introduction of biologic therapies targeting key pathways of the natural and adaptive immune response such as Tumor Necrosis Factor α (TNF-α) inhibitors (i.e. Infliximab, IFX; Adalimumab, ADA; Golimumab, GOL; Certolizumab Pegol, CTZ) and, more recently, integrin-receptor antagonists. Among them, Vedolizumab (VDZ) has been recently approved for use by FDA and EMA in patients with moderate-to-severe IBD who are intolerant or refractory to either conventional therapy or a TNF-α inhibitor. VDZ is a monoclonal antibody blocking the α4β7 integrin which is selectively expressed by the vascular endothelium in the gastrointestinal tract [7]. With the introduction of VDZ, a biologic treatment targeting novel IBD-relevant biologic pathways, it is crucial to understand how to integrate such innovations into current clinical practice. The following report concerns the role of VDZ for the treatment of UC and CD.

2. Methodology

A panel of 14 Italian experts in IBD management held a roundtable discussion in November 2014. A facilitator (LN) presented the relevant literature from published guidelines to the panel of experts as a trigger to enhance discussion. Panelists were then prompted to express their opinion on the following themes:

1. Definitions and grading of disease activity, treatment response, remission, relapse and recurrence of disease, steroid-refractory and steroid-dependent disease, treatment failure, primary and secondary failure in patients treated with TNF-α inhibitors.
2. Patient Profiling and Case Management in clinical practice.
3. Role of VDZ for induction of remission in UC and CD.
4. Role of VDZ for maintenance of remission in UC and CD.
5. Update of treatment algorithms.

A classic focus group approach was undertaken to encourage participation of all members and highlight potential areas of disagreement. If consensus had not been reached at the first round, panelists were asked to discuss reasons for disagreement. When divergence could not be sorted out, disagreement was noted.

The discussion was recorded and summarized in an intermediate report. Based on expert opinions and literature review, a restricted steering committee drafted tentative recommendation statements. Definitions adopted in the current expert consensus report are described in Appendix 1. We graded evidence levels and strengths of recommendations based on the Oxford classification system [8].

The panel of opinion leaders joined a second roundtable meeting in March 2015. Panelists were prompted to rate their agreement with all recommendation statements (yes/no). If consensus had not been reached at the first round, panelists were asked to reformulate the statements. Statements have been reformulated in repeated discussion rounds until experts had reached complete agreement on every statement.

3. Current biologic therapy for IBD patients with moderate-to-severe activity

Several guidelines and consensus reports concerning the management of IBD have been published in the past 5 years [9–15]. While corticosteroids are effective inducers of remission, they must not be used for maintenance being ineffective and potentially harmful [16]. Additionally, a large share of patients are either refractory or dependent to corticosteroids [16]. Maintenance with conventional immunosuppressive agents is effective yet hampered by potential side effects [17,18]. The traditional approach to biologic therapy for IBD involved the inhibition of adaptive immunity pathways through TNFα-blockage. Biologic therapy with TNF-α inhibitors has proven effective in inducing and maintaining remission in patients with IBD, reduced the need for surgery in patients who are intolerant or not responding to conventional therapy and it has shown significant steroid-sparing effect [19–24]. The efficacy outcomes reported in randomized controlled trials (RCTs) of current biologic therapy in UC and CD are summarized in Table 1. Results from meta-analyses of RCTs suggest that no individual TNF-α inhibitor offers clear advantage over the others [21–23].

Table 1
Synopsis of efficacy outcomes of pivotal RCTs of biologic therapy in patients with IBD.

RCT (molecule)	Clinical response	Enhanced clinical response	Clinical remission	Mucosal healing	CS-free remission	Durable clinical response	Durable clinical remission
UC: Induction							
GEMINI 1 (VDZ)[a]	47%	–	17%	41%	–	–	–
ACT 1 (IFX)	69%	–	39%		–	–	–
ACT 2 (IFX)	65%	–	34%		–	–	–
ULTRA 1 (ADA)	55%	–	19%	47%	–	–	–
ULTRA 2 (ADA)	59%	–	21%	49%	–	–	–
PURSUIT 1 (GOL)	51%	–	18%	42%	–	–	–
UC: Maintenance							
GEMINI 1 (VDZ)[a]	–	–	42%	52%	31%	57%	20%
ACT 1 (IFX)	46%	–	35%	45%	–	–	–
ULTRA 2 (ADA)	37%		22%	31%			
PURSUIT 2 (GOL)	47%	–	23%	42%	28%	–	–
CD: Induction							
GEMINI 2 (VDZ)[a]	48%	31%	15%	–	–	–	–
GEMINI 3 (VDZ – 6 weeks)[a]	–	39%	19%	–	–	–	–
GEMINI 3 (VDZ – 10 weeks)[a]		48%	29%	–	–	–	–
Targan et al. (IFX)	81%	–	33%	–	–	–	–
ACCENT 1 (IFX)	58%	–	–	–	–	–	–
CLASSIC 1 (ADA)	59%	40%	24%	–	–	–	–
CHARM[a] (ADA)	58%	–	–	–	–	–	–
CD: Maintenance							
GEMINI 2 (VDZ)[a]	39%	44%	–	–	32%	–	21%
ACCENT 1 (IFX)	–	–	29%	–	28%	–	–
CHARM[a] (ADA)	–	–	36%	–	29%	–	–

[a] GEMINI 1, 2, 3 and CHARM enrolled patients with previous exposure to TNF-α inhibitors.

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Power calculation based on the results of a network meta-analysis suggests that head-to-head trials across TNF-α inhibitors would require over 3000 patients, given the expected small effect size of the comparison [22]. For this reason the choice of the first biologic treatment should be tailored to the individual patient based on treatment history, symptoms pattern, local practice and preference.

Despite proven effective, rates of primary non-response to TNF-α inhibitors in RCTs range between 20 and 40% [7], whereas observational studies report up to 25% non-response rates [25]. Furthermore, up to 40% of patients initially responding to TNF-α inhibitors develop intolerable side-effects or lose response over time [26,27]. One of the main causes of reducing efficacy in former respondents is the development of neutralizing antibodies mostly occurring within the first 6 months of treatment in up to 40% of patients [28]. Anti-drug antibodies (ADAb) are associated with infusion reactions, injection site reactions and delayed serum sickness reactions [29].

A meta-analysis of RCTs showed that patients with UC receiving IFX had 52% increased risk of developing any adverse event during treatment [24]. According to post-marketing observational reports and randomized controlled trials, the incidence of serious infections, as well as TBC reactivation, might be higher [26,30–33] in patients receiving TNF-α inhibitors. In one registry study, IFX was associated with 90% increase in mortality risk compared to placebo [34], yet the causative role of IFX was not proven. Additionally more recent studies showed no excess mortality risk associated with IFX [33,35]. The causal relationship between TNF-α inhibitors and other serious adverse events such as cancer, drug-related lupus and psoriasis-like eczema is not sufficiently proven to date [36–40]

Until the introduction of VDZ there was no alternative to TNF-α inhibitors in patients who were intolerant, dependent or failing with conventional therapy. Furthermore, dose escalation or switching to other TNF-α inhibitors were the only alternative medical options in patients who failed with biologic treatment. In the following sections we report the position of the consensus panel and evidence supporting recommendations.

3.1. Vedolizumab

VDZ, a biological agent blocking the α4β7 integrin, has been demonstrated effective in inducing and maintaining remission among patients with moderate-to-severe CD and UC [41,42]. The mechanism of action of VDZ is unique among the biologic therapies available for treatment in IBD patients. VDZ selectively binds to α4β7-ntegrin [7]. Pharmacodynamics studies demonstrated that VDZ exclusively inhibits the trafficking of α4β7-ntegrin-expressing T-cells from blood vessels to the intestinal mucosa without interfering with other inflammatory or immunological processes [43].

VDZ has shown good acceptability and safety, elevated receptor saturation, minimal immunogenicity and ADAb formation in phase I and phase II trials [44–46]. The efficacy and safety of VDZ in UC and CD has been demonstrated against placebo in three pivotal phase III RCTs (GEMINI 1, GEMINI 2 and GEMINI 3) evaluating patients with moderate-to-severe UC or CD who had previously failed at least one prior therapy (e.g. corticosteroids, immunomodulators, TNF-α inhibitors) [47–49]. A fourth open-label, long-term efficacy and safety RCT, the GEMINI LTS is ongoing and is expected to release final results after March 2016. In the GEMINI I study, VDZ showed a clear advantage over placebo in inducing clinical response (Δ = 22%, 95%CI: 12–32%), clinical remission (Δ = 12%, 95%CI: 5–18%), and mucosal healing (Δ = 16%, 95%CI: 6–26%) at 6-week in UC patients with no or prior exposure to TNF-α-blockers. Despite proven effective in both subgroups, efficacy was higher among TNF-α inhibitors naïve patients [47]. Additionally, the GEMINI I maintenance study demonstrated that VDZ achieved better long-term outcomes (52 weeks) compared to placebo in terms of clinical remission rate, durable clinical response and remission, mucosal healing, and steroid-free remission [47]. Again, despite effective in both subgroups, VDZ achieved slightly better outcomes among TNF-α inhibitors naïve patients compared to those previously exposed [47].

The efficacy and safety of VDZ among CD patients were demonstrated in phase II and phase III RCTs. A recent meta-analysis pooling data from Phase II and Phase III trials in CD patients [50] showed that VDZ increased CDAI-100 response and clinical remission in induction therapy for patients with active CD despite it failed to meet some of the primary endpoints in the GEMINI 2 and GEMINI 3 studies [48,49]. Additionally, induction with VDZ provided significant benefits in terms of CDAI-100 response and clinical remission at week 10 both among TNF-α inhibitors failure and in TNF-α inhibitors naïve patients (GEMINI 3) [49]. Finally, GEMINI 2 maintenance study demonstrated higher clinical remission, enhanced clinical response and corticosteroid sparing rates among patients treated with VDZ compared to placebo in the overall cohort and in TNF-α inhibitors naïve patients [48]. Finally, in a secondary analysis of GEMINI 2, VDZ achieved improved healing rates of fistulizing disease [48].

Pooled safety analysis from 5 RCTs had shown that VDZ was not associated with increased rates of any serious adverse effects (RR: 1.21; 95%CI: 1.00–1.46), serious infections (RR: 1.17; 95%CI: 0.51–2.69) and other adverse events including progressive multifocal leukoencephalopathy (PML), death, and cancer [50].

Health authorities and clinicians raised concern about the possible risk of progressive multifocal leukoencephalopathy (PML), a disease caused by reactivation of JC virus in the central nervous system in patients treated with integrin antagonists. The seroprevalence of JC virus was 65% in a sample of patients with Crohn's Disease [51]. Natalizumab, the early precursor of integrin-blocking monoclonal antibodies, exhibits a systemic suppression of T-cells migration and is associated with increased risk of PML in patients with previous central nervous system (CNS) infection by JC virus [52]. The risk of natalizumab-related PML was associated with the inhibition of CNS immune surveillance system [52]. However, contrary to natalizumab, VDZ specificity of action for the intestinal tract was clearly demonstrated in animal models of the disease and human healthy volunteers [53]. Gut-specificity is thought to be a key property for the safety of integrin-blocking drugs [53].

The 4-year incidence of PML in patients treated with natalizumab who had JC-antibodies at treatment onset was 1.1% among those receiving prior immunosuppression and 0.5% among those without prior exposure to immunosuppressants [54]. On the contrary, no cases of PML were diagnosed in VDZ RCTs population, approximately 3000 patients exposed for a median time of 18 months of whom 80% had prior exposure to immunosuppressant [50]. Such results are confirmed by post-marketing pharmacovigilance data obtained from over 3000 patients exposed to the drug in clinical setting. Despite studies with longer follow-up are needed, such data do not suggest any VDZ-related risk of PML or JC reactivation.

4. Patient's profiling and case management

4.1. Induction of remission in Ulcerative Colitis

A large share of patients with moderate-to-severe UC do not achieve long-term remission under conventional treatment [55–58], while up to 40% do not respond to the first TNF-α inhibitors induction therapy [26,59] and up to 40% of primary responders to TNF-α inhibitors lose response over time [60]. Additionally, both conventional treatments and TNF-α inhibitors are burdened with

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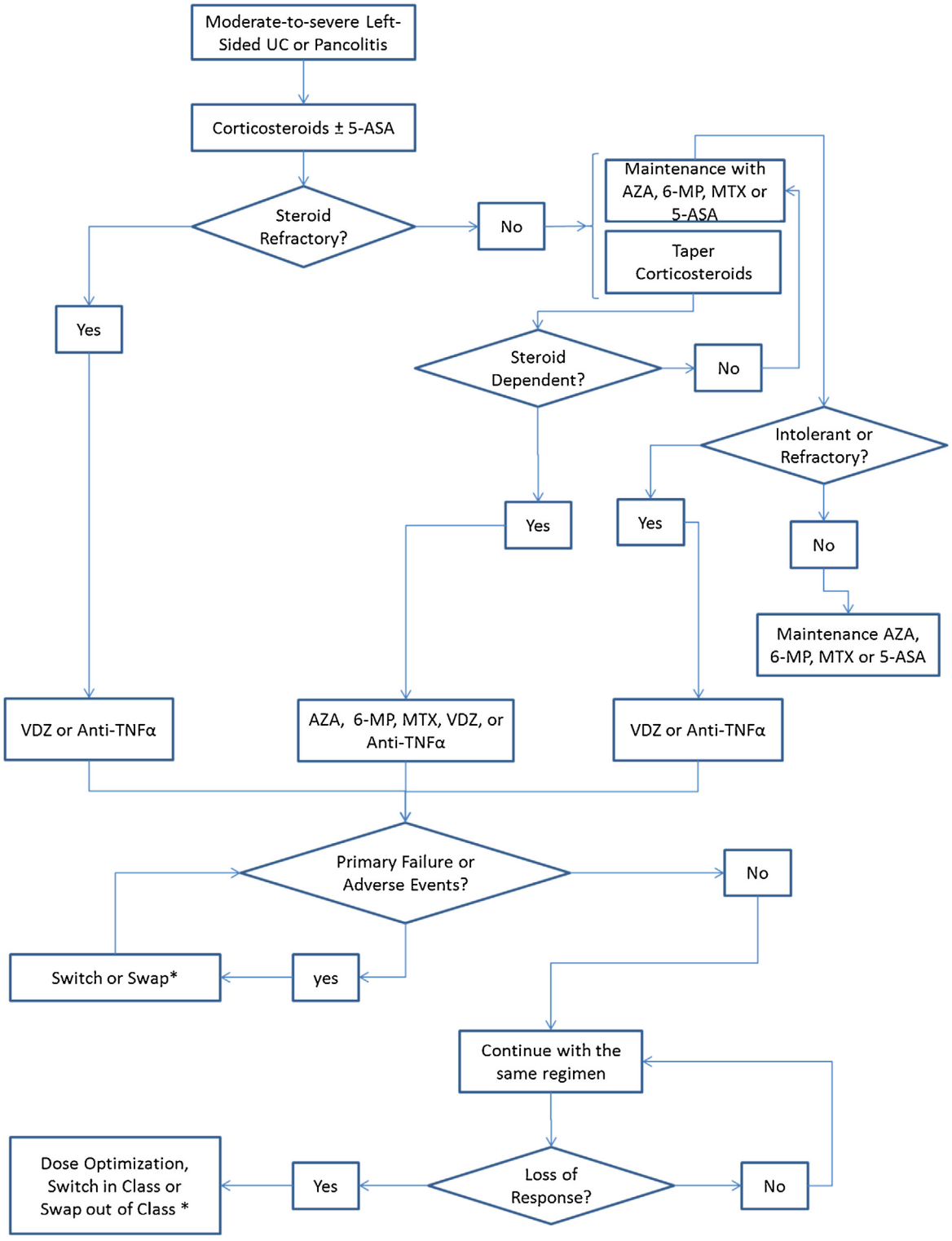

Fig. 1. Treatment algorithm: induction and maintenance of remission in moderate-to severe UC. *Notes*: *Swap to be preferred in case of paradoxical inflammation associated with anti-TNFα treatment. In case of ongoing serious infection, stop treatment with biologic therapy or immunosuppression until infection is eradicated.

adverse events [25,26,30,61]. The proposed treatment algorithm is represented in Fig. 1.

4.1.1. VDZ for induction of remission in UC patients with moderate-to-severe activity

Epidemiologic studies showed that younger age at onset is associated to more aggressive initial course and higher risk of colectomy [62,63]. TNF-α inhibitors may cause serious adverse events in older patients [64,65]. Ongoing RCTs are evaluating the efficacy and safety of VDZ in pediatric patients. Sub-group analysis from GEMINI 1, which uniquely permitted a wide age range for enrollment (18–80 years) among RCTs for UC management, has shown that VDZ is effective and safe among elderly patients [47].

Patients with extensive disease face higher risk of colectomy and extra-intestinal manifestations. The RCTs evaluating the effectiveness and safety of VDZ and TNF-α inhibitors included a large

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share of patients with moderate-to-severe pancolitis [47,66–69]. Therefore, VDZ and TNF-α inhibitors should be considered first-line options in patients with moderate-to-severe pancolitis who do not respond to conventional therapy.

Summary of recommendations

- *First-line treatment for moderately-to-severely active left-sided colitis or pancolitis in patients who are intolerant or do not respond to conventional therapy include either VDZ or TNF-α inhibitors (EL1a, RGA).*
- *Given its favorable safety profile, VDZ should be preferred for patients with higher risk of opportunistic infections such as (but not restricted to) elderly patients (≥65 years of age) (EL1b, RGA).*

4.1.2. Patients with previous steroid treatment failure, refractory to immune-modulator maintenance therapy, and refractory to TNF-α inhibitors

An important aspect of decision-making is patients' treatment history. Steroid-refractory disease occurs in a large share of patients [70]. Previous guidelines recommended the use of TNF-α inhibitors or thiopurines in steroid-refractory and steroid-dependent patients [10–15]. Similarly, VDZ has proven effective in inducing remission among outpatients with moderate-to-severe UC who are steroid-refractory [47]. Additionally, in the GEMINI I study, VDZ showed favorable outcomes in terms of clinical response, clinical remission and mucosal healing rate among TNF-α inhibitors naïve and in patients who were either primary or secondary non-responders to TNF-α inhibitors [47]. Direct comparisons between VDZ and TNF-α inhibitors drugs are not available. Furthermore comparisons across trials are made difficult due to differences in the distribution of key patients' characteristics and definitions of endpoints. A recent network meta-analysis showed that VDZ and TNF-α inhibitors have similar efficacy against placebo [23]. However VDZ had superior safety profile [23], a finding that must be confirmed in studies with longer follow-up times. Finally, all RCTs on biologic treatment included a large share of patients with moderate-to-severe UC despite immune-modulator maintenance therapy. In the GEMINI 1 study, only 30% of patients did not receive corticosteroids or azathioprine (AZA) and no RCT has reported subgroup analyses in this patient-group [47].

Summary of recommendations

- *VDZ and TNF-α inhibitors should be considered alternative first-line treatment for patients with active moderate-to-severe UC in patients who are persistently refractory or intolerant to immune-modulator therapy (EL1b, RGA).*
- *Among TNF-α inhibitors naïve patients, VDZ and TNF-α inhibitors should be considered alternative first-line induction treatment for patients with active moderate-to-severe UC despite concurrent adequate treatment with steroids (EL1b, RGA).*
- *VDZ should be considered for induction treatment in patients with active moderate-to-severe UC who are refractory or intolerant to TNF-α inhibitors (EL1b, RGA).*
- *VDZ (EL1b, RGA), and TNF-α inhibitors (EL1b, RGA) should be considered alternative first-line induction treatment as steroid-weaning therapies for patients with active moderate-to-severe steroid-dependent UC.*

4.2. Maintenance therapy in patients with moderate-severe UC

Sustained mucosal healing in the first year post-induction is associated with better long-term outcomes and reduced risk of colectomy [23]. Hence, the goal of maintenance therapy is steroid-free clinical and endoscopic remission. Despite effective for many patients, about half of patients treated with maintenance therapy have a relapse within 1 year after successful induction [65–68,71]. In population-based studies, the 5-year prevalence of patients with at least 1 relapse was 87% [72]. Data from the placebo arms of RCTs show that without a maintenance treatment, relapse rate at 1-year may be as high as 80% [46,65–68,71]. Disease course studies showed that the likelihood of future flares is associated with history of frequent relapses, extra-intestinal manifestations, younger age, persisting mucosal inflammation and psychological distress [73,74]. Additionally non-adherence to maintenance therapy is associated with a strong increase in relapse rates [75]. Non-adherence to maintenance therapy occurs in about 30–45% of patients with conventional therapy [76] and 20–30% of patients taking TNF-α inhibitors [77]. Risk factors for non-adherence include regimen complexity, mode of administration, concomitant immunomodulators, and side effects [78,79].

4.2.1. VDZ as maintenance therapy in patients with moderate-severe UC

Previous guidelines recommended continuation with the same biologic drug in patients achieving clinical response or remission with TNF-α inhibitors [10–14]. The results of the GEMINI I study indicate that such recommendation should be extended to patients initially treated with VDZ [46]. The maintenance study of VDZ have shown promising outcomes: among patients responding to induction therapy, 52–56% achieve sustained mucosal healing, 42–45% were in clinical remission after 52 weeks, and 31–45% were in steroid-free remission; the effectiveness concerning all such endpoints was more pronounced in TNF-α inhibitors naïve patients; finally, clinical remission and durable clinical response was 36–40% and 44–46%, respectively, in patients with previous exposure to TNF-α inhibitors [46].

In population-based studies, steroid-dependent subjects represent 20–30% of patients [15,55]. In such cases, AZA has demonstrated increased clinical remission rates compared to 5-aminosalicylic acid (5-ASA) [80]. There are no direct comparisons between AZA and biologic treatment. Both TNF-α inhibitors and VDZ demonstrated better efficacy than placebo among patients with moderate-to-severe UC despite concurrent steroid-therapy [46,66–68]. In the GEMINI 1 study, about 30% of patients with baseline corticosteroid therapy achieved corticosteroid free remission at 52 weeks among those treated with VDZ [46].

4.3. Induction of remission in patients with moderate-to-severe Crohn's Disease

Symptom-based assessment of disease activity is prone to classification error given that clinical appearance in CD patients may be partly explained by disease extension, concurrent diseases or intestinal complications and previous surgery [81]. Therefore, objective evidence of disease activity should be obtained (inflammatory markers, cross-sectional imaging or colonoscopy as appropriate) before starting or changing medical therapy. Treatment choices for patients with CD should take into account disease activity, the anatomical localization of lesions, the behavior of disease, and previous response to treatment (especially when considering the treatment of relapses, as well as the treatment of steroid-dependent or steroid-refractory disease). Treatment prescriptions should be customized according to factors that predict progressive course. Epidemiologic studies have shown that younger age at onset and perianal fistulas are associated with poorer long-term outcomes [82,83]. Additionally endoscopic finding of deep ulcers, anorectal or extensive disease, severe extra-intestinal manifestations, upper gastrointestinal involvement, elevated C-Reactive Protein (CRP), elevated fecal calprotectin and smoking habit are associated with more aggressive and

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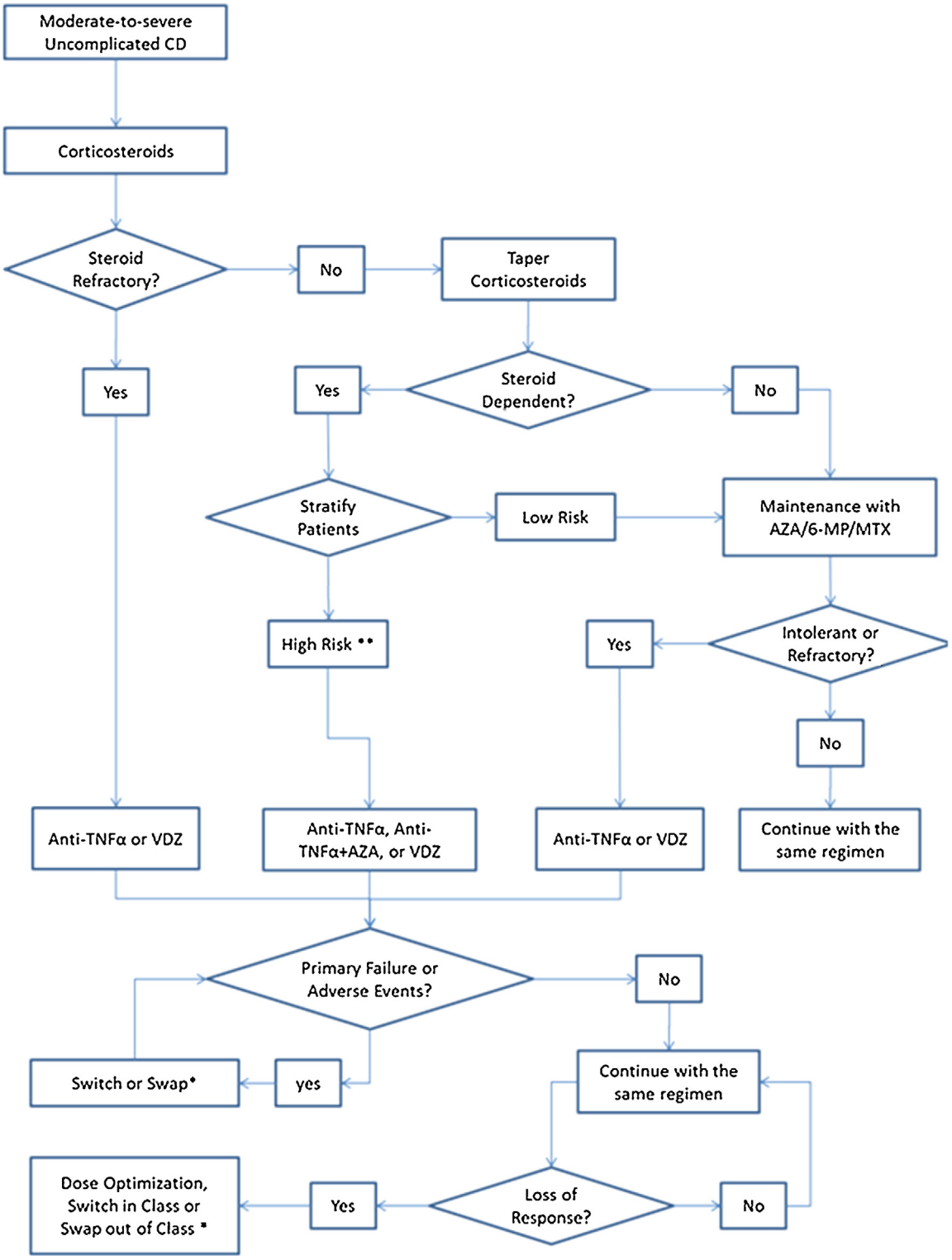

Fig. 2. Treatment algorithm: induction and maintenance of remission in moderate-severe CD. *Swap to be preferred in case of paradoxical inflammation associated with anti-TNFα treatment. In case of ongoing serious infection, stop treatment with biologic therapy or immunosuppression until infection is eradicated. **High risk patients defined by age and short disease duration plus any of Perianal disease, Deep ulcers, Upper GI disease, Anorectal or Extensive disease, Severe EIMs.

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complicated course of disease [84]. The proposed treatment algorithm is represented in Fig. 2.

Summary of recommendations

- *In patients achieving remission after induction with VDZ, continuation with the same drug is appropriate for at least 1-year (EL1a, RGA).*
- *AZA (EL1b, RGA), VDZ (EL1b, RGA) and TNF-α inhibitors (EL1b, RGA) should be considered first-line maintenance treatment as steroid-weaning therapies for patients with moderate-to-severe steroid-dependent UC.*

4.3.1. VDZ for the induction therapy in patients with moderate-to-severe uncomplicated Crohn's Disease

Systemic corticosteroid remains the initial treatment option in this group of patients based on cost-effectiveness considerations [11–15]. Despite AZA has merits as steroid-sparing therapy, its slow action makes it unsuitable for a monotherapy as induction treatment [85]. Data from clinical trials indicate that VDZ is effective in the induction phase among patients with moderate-to-severe luminal disease despite concurrent treatment with conventional therapy and/or TNF-α inhibitors [48,49]. In the GEMINI II and GEMINI III trials the pharmacologic action of VDZ occurred at 10 weeks in a significant share of patients [48,49]. Hence, induction with VDZ might be extended to 10 weeks in patients with partial response in the first 6 weeks.

Comparisons across biologic treatments are difficult due to the heterogeneity between inclusion and exclusion criteria in RCTs and endpoint definition as well [86]. Contrary to RCTs of IFX, ADA e CTZ, all patients enrolled in the GEMINI CD trials presented signs of systemic inflammation [48,49]. A network meta-analysis showed that all biologic agents were superior to placebo for induction [87].

Additionally, GEMINI II and III trials showed that VDZ is effective in patients with previous or current failure with TNF-α inhibitors and among those with moderate-to-severe activity despite the use of TNF-α inhibitors [48,49]. Hence, VDZ might be used as a second line induction treatment after primary failure with TNF-α inhibitors.

Summary of recommendations

- *VDZ and TNF-α inhibitors are treatments of choice in low-risk patients with active moderate-to-severe, luminal, uncomplicated CD who have failed or are intolerant to conventional treatment (EL1a, RGA).*
- *VDZ (EL1b, RGA), TNF-α inhibitors (EL1a, RGA) are treatments of choice as steroid-weaning therapy, in patients with steroid-dependent active moderate-to-severe uncomplicated.*
- *VDZ is the treatments of choice in patients with active moderate-to-severe uncomplicated CD who have failed or are intolerant to TNF-α inhibitors (EL1a, RGA).*

The choice of the first biologic treatment should be tailored to the individual patients as no clear advantage of one option over the competitors exists in term of efficacy (EL1b RGA).

4.3.2. VDZ as maintenance therapy in moderate-to-severe uncomplicated Crohn's Disease

The choice of maintenance treatments in patients with medically induced remission should be based on the general evaluation of the disease, the presence of prognostic factors suggesting an aggressive disease course (type of initial presentation, frequency, and severity of flares), the extent of disease and the effectiveness and tolerance of treatments previously administered for induction of remission or maintenance. Other factors such as the presence of biological or endoscopic signs of inflammation and the potential for complications should also be considered.

Despite effective for induction, exposure to prednisolone should be tapered in few weeks after successful induction since steroids do not provide effective maintenance and their use is associated with substantial side effects [11–15]. In a meta-analysis of RCTs, maintenance with corticosteroids did not reduce the risk of relapse compared to placebo [88]. AZA is effective in maintaining remission in patients with luminal CD [89]. Among AZA-responders, only 40% of patients maintain the initial response at 10-year follow-up and the clinical benefits in term of reduced hospitalization, disease activity and surgery rates might be offset by increased risk of malignancies and side effects [90].

All trials concerning biologic therapies included a significant share of patients with moderate-to-severe uncomplicated CD despite concurrent treatment with traditional therapy [48,49,90]. Additionally, the GEMINI CD trials enrolled patients with and without previous exposure to TNF-α inhibitors [48,49]. Data from clinical trials show that VDZ was effective in maintaining clinical remission (39% vs 22%), CDAI-100 response (44% vs 30%), steroid-free remission (32% vs 16%) and durable remission (21% vs 14%) at 52-week after treatment onset. In a recent network meta-analysis, both biologic and conventional treatments were superior to placebo for maintenance. Pair-wise comparisons yielded mixed results: ADA and the combination of IFX + AZA regimens were superior to certolizumab and AZA/6-mercaptopurine. VDZ appeared to be as effective as IFX and IFX + AZA but less effective that ADA for maintenance therapy [87]. However, it should be noted that patients enrolled in the GEMINI CD studies included a large share of patients who were resistant to TNFα-antagonist and conventional therapy as well, making it difficult to compare results [48,49,86]. Of note, in a recent meta-analysis of treatment durability, withdrawal rates due to side effects were smaller for VDZ compared to AZA, 6-mercaptopurine and TNF-α inhibitors [91] while the rate of serious adverse events was not greater than placebo [48,49].

Summary of recommendations

- *In patients achieving remission after induction with VDZ, continuation with the same drug is appropriate for at least one year (EL1b, RGA).*
- *In steroid-dependent or steroid-intolerant patients, either VDZ, ADA, IFX alone or in combination with AZA should be considered for maintenance (EL1a, RGA).*
- *VDZ or TNF-α inhibitors should be considered for patients who are not-responding or intolerant to AZA or who experience a relapse during AZA maintenance (EL1a, RGA).*

4.3.3. Fistulizing CD

Data from the GEMINI CD studies have shown that VDZ is effective in promoting fistula closure in 46% of patients compared to 11% in the placebo arm [48,49]. However, contrary to previous experience with IFX [90], no study evaluated the efficacy and safety of VDZ after surgery in such patient group.

Summary of recommendations

- *Fistulizing CD may be treated by a combination of surgical treatment and IFX infusions (EL1c RGA).*
- *ADA and VDZ have shown to be effective in the treatment of fistulizing CD in observational studies and subgroup analysis of RCT respectively, but there is no definitive evidence from RCTs of effectiveness and safety in combination with surgical procedures (EL2a RGB).*

Please cite this article in press as: Armuzzi A, et al. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.12.018
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4.4. Secondary loss of response or intolerance to TNF-α inhibitors among UC and CD patients

Treatment of relapses after successful induction and maintenance therapy is a controversial aspect of care. Approximately 40% of patients lose response to TNF-α inhibitors over time [39,92]. Unfortunately, beside smoking, there is no clear risk factor of secondary loss of response (LoR) to TNF-α inhibitors. However, it has been shown that the combination of IFX and AZA might lead to prolonged effect and reduced ADAb formation compared to the administration of IFX alone [93]. Few epidemiological studies investigated differential LoR rates in CD patients on TNF-α inhibitors. Current evidence suggests that higher rates of LoR occur among patients maintained with ADA compared to those on IFX [94,95]. However, more patients in the ADA group were not naïve to TNF-α inhibitors.

Until the introduction of VDZ, the options for induction of remission in patients experiencing LoR to TNF-α inhibitors were restricted to dose optimization (i.e. increasing the dose or reducing administration intervals), adjunction of immunosuppressants or switching to a different TNF-α inhibitor in the attempt to avoid surgery [28]. Data from clinical trials and real life studies show that 50–88% of patients who had initially responded to IFX but lost response during maintenance therapy, regained response by increasing the dose [39,96]. Switching to a different treatment is effective to regain response in only 50% of cases [97]. In patients experiencing a LoR to ADA, dose optimization re-establishes clinical response in about 70% of patients [92].

Despite dose optimization and switching may allow to regain remission in a sizeable fraction of patients, both strategies are subject to suboptimal outcomes and increased health-care costs [39,92]. Tailoring dosing regimens and switching strategies on the assessment of anti-TNF-α antibodies titles and drug trough levels, is a promising strategy [39,92]. However, the lack of standard analytical methods limits its suitability in clinical practice.

Additionally, the efficacy of VDZ as a second-line treatment has been demonstrated given its superiority over placebo in patients with moderate-to-severe IBD despite concurrent or no previous exposure to TNF-α inhibitors. However, there currently is no evidence about the best strategy to manage patients with secondary failure to TNF-α inhibitors in patients with IBD. Evidence from other therapeutic areas suggests that swapping to a different pharmaceutical class after a first episode of LoR is associated with large drug survival benefits compared to switching strategies irrespective of the underlying cause of secondary failure [98].

Finally, VDZ demonstrated a promising safety profile in RCTs, characterized by a low rate of infections [50] possibly due to its exclusive gut selectivity [53] among patients with refractory or intolerant to TNF-α inhibitors. For these reasons, swapping strategies should be preferred in case of severe adverse events such as paradoxical inflammation or severe infections occurring during TNF-α inhibitors treatment.

Summary of recommendations

- *Current management strategies for patients who either lose response or become intolerant to anti-TNFα therapy include dose optimization or switching within biologic class (EL1b, RGA).*
- *Indirect evidence suggests that swapping to a different biologic class might be an alternative management strategy in patients loosing response or being intolerant to TNF-α inhibitors; however, additional evidence in IBD patients is needed before recommending such strategy as the preferred management option in this patients' group (EL5, RGD).*
- *Swapping should be considered the preferred management strategy in patients experiencing serious drug-related adverse events (such as paradoxical inflammation) during treatment with TNF-α inhibitors (EL1b RGA).*

5. Conclusions

The introduction of biological therapy improved clinical and patient-reported outcomes for many patients who did not benefit from conventional therapy. However, despite treatment with TNF-α inhibitors, a sizeable share of patients still face suboptimal outcomes due to primary or secondary therapy failures. VDZ, the new α4β7-integrine receptor antagonist, provides a valuable option for IBD patients and represents a welcomed addition to current treatment alternatives.

Along with other biologic agents, VDZ should be considered first-line induction and maintenance treatment for steroid-dependent and steroid-refractory patients, or those who do not achieve stable remission with immunomodulators. Despite data from RCTs are not directly comparable due to differences in enrollment criteria and endpoint definitions, evidence shows no clear advantage of any biologic therapy over competitors, so far. Hence, the choice of the first biologic agent should be tailored to the individual patient based on clinical manifestations of the disease, treatment and disease course age, and drug safety profile. Given the promising long-term efficacy and safety outcomes shown in RCTs, VDZ should be continued for maintenance for at least one year after successful induction in both UC and CD patients.

Finally, VDZ has proven effective and safe in patients failing previous treatment courses with TNF-α inhibitors. As a consequence, VDZ should also be considered a valid second-line treatment for primary and secondary failures to TNF-α inhibitors. The current management schemes addressing loss of response to TNF-α inhibitors entail dose optimization and treatment switches within class. Such schemes were motivated by the lack of viable alternatives. Despite no direct evidence in IBD patients is available to date, data from other therapeutic areas suggest that swapping to medications with a different mechanism of action after the first treatment failure might provide improved outcomes. Given the promising safety profile of VDZ, this might be particularly relevant for patients who experience serious side effects during TNF-α inhibitors treatment (e.g. infectious diseases or paradoxical inflammation).

Conflict of interest

Sandro Ardizzone, MD; consultant for Abbott Laboratories, MSD, Nycomed.

Alessandro Armuzzi, MD, Consultant and Lecture fee(s) from: Abbvie, Astra-Zeneca, Chiesi, Ferring, Hospira, MSD, Otsuka, Takeda, Zambon; Consultancy for: Abbvie, Hospira, Lilly, MSD, Mundipharma, Sofar, Takeda; Grant for research from MSD.

Fabiana Castiglione, MD; Advisory boards of Abbvie, MSD, Hospira, Takeda. Lecture fees from: Chiesi, Abbvie.

Silvio Danese, MD; consultant and advisory board member for Schering-Plough, Abbott Laboratories, Merck & Co., UCB Pharma, Ferring, Cellerix, Millennium Takeda, Nycomed, Pharmacosmos, Actelion, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson.

Marco Daperno, MD; Advisory boards of: Abbvie, MSD, Hospira, Takeda; he received grants for Lectures from: Chiesi, SOFAR, Ferring.

Massimo Fantini, MD; has received consultancy fees from Takeda.

Gionata Fiorino, MD; Consultant and a member of Advisory Boards for MSD, Takeda Pharmaceuticals, and Janssen Pharmaceuticals.

Please cite this article in press as: Armuzzi A, et al. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.12.018
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Giuseppe Frieri, MD; received consultancy fee from Takeda Pharmaceuticals.

Paolo Gionchetti; Speaker, consultant or advisory board member for Abbvie, MSD, Ferring, Takeda, Nycomed, Sofar, Chiesi, Hospira.

Luca Neri, MD, has received consultancy fees from Abbvie, Takeda, Shire, Angelini, DoxaPharma, BMS, Fresenius Medical Care.

Ambrogio Orlando, MD; Advisory board of Abbvie, MSD, Hospira, Takeda. Lecture fees from: Abbvie, Chiesi, SOFAR, Ferring.

Fernando Rizzello, MD; Consultant for Abbvie, Takeda, MSD; lecture fees/educational grants from Abbvie, Takeda, MSD, Sofar, Ferring, Chiesi.

Maria Lia Scribano, MD; consultancy fees from Biogen Idec, Takeda, Mundipharma; lecture fees from Zambon.

Giacomo Carlo Sturniolo, MD; consultancy fees from SEDA, PLS, DoxaPharma, Takeda; lecture fees from Scharag, Sofar, Otsuka, Uvet.

Maurizio Vecchi, MD; has received consultancy fees from Giuliani, Schering-Plough, Abbvie, MSD, Ferring, Takeda, Nycomed, Cosmo Pharmaceuticals, Sofar, Chiesi, Hospira, Otsuka.

Funding

None.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.12.016.

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Please cite this article in press as: Armuzzi A, et al. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.12.016
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