

Post-Marketing Safety Experience of Vedolizumab in Patients Receiving Concomitant Treatment with Other Biologics

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Background

- Vedolizumab (ENTYVIO[®]) is a humanized monoclonal antibody targeting $\alpha_4\beta_7$ integrin that is approved for the treatment of moderately to severely active Crohn's disease (CD) and ulcerative colitis (UC) in adults.^{1,2}
- Concomitant use of other biologics with vedolizumab is not recommended in the vedolizumab prescribing information¹ and has not been evaluated in clinical trials, meaning that safety data are limited on patients receiving this combination.
- We compared 4 years of post-marketing safety data collated by Takeda Pharmaceutical Company Ltd (Takeda) on patients receiving vedolizumab and concomitant biologics with patients receiving vedolizumab and non-biologic concomitant therapy.

Methods

- All post-marketing adverse event (AE) reports received by the licence holder, Takeda, since the date of first approval of vedolizumab (20 May 2014) are held in the Vedolizumab Global Safety Database; their sources include:
 - spontaneous reports from patients, healthcare professionals and regulatory authorities
 - solicited reports from patient support and market research programmes
 - reports extracted from the literature.
- AE reports received between first approval of vedolizumab and 19 May 2018 that contained data on concomitant medication use were identified for review, using search terms from the Medical Dictionary for Regulatory Activities version 21.0.
- Patients reporting concomitant medication use were stratified into two groups:
 - patients receiving vedolizumab with concomitant biologics (and additional non-biologic treatments in some cases, including corticosteroids or other non-biologic immunomodulators)
 - patients receiving vedolizumab with concomitant non-biologic therapy (including corticosteroids or other non-biologic immunomodulators).
- Data on patients who were not reported to have received any form of concomitant treatment were also collated, but were not analysed here.
- The estimated global vedolizumab exposure in the post-marketing setting was calculated based on the number of vials shipped worldwide, assuming 8-week dosing intervals.

Results

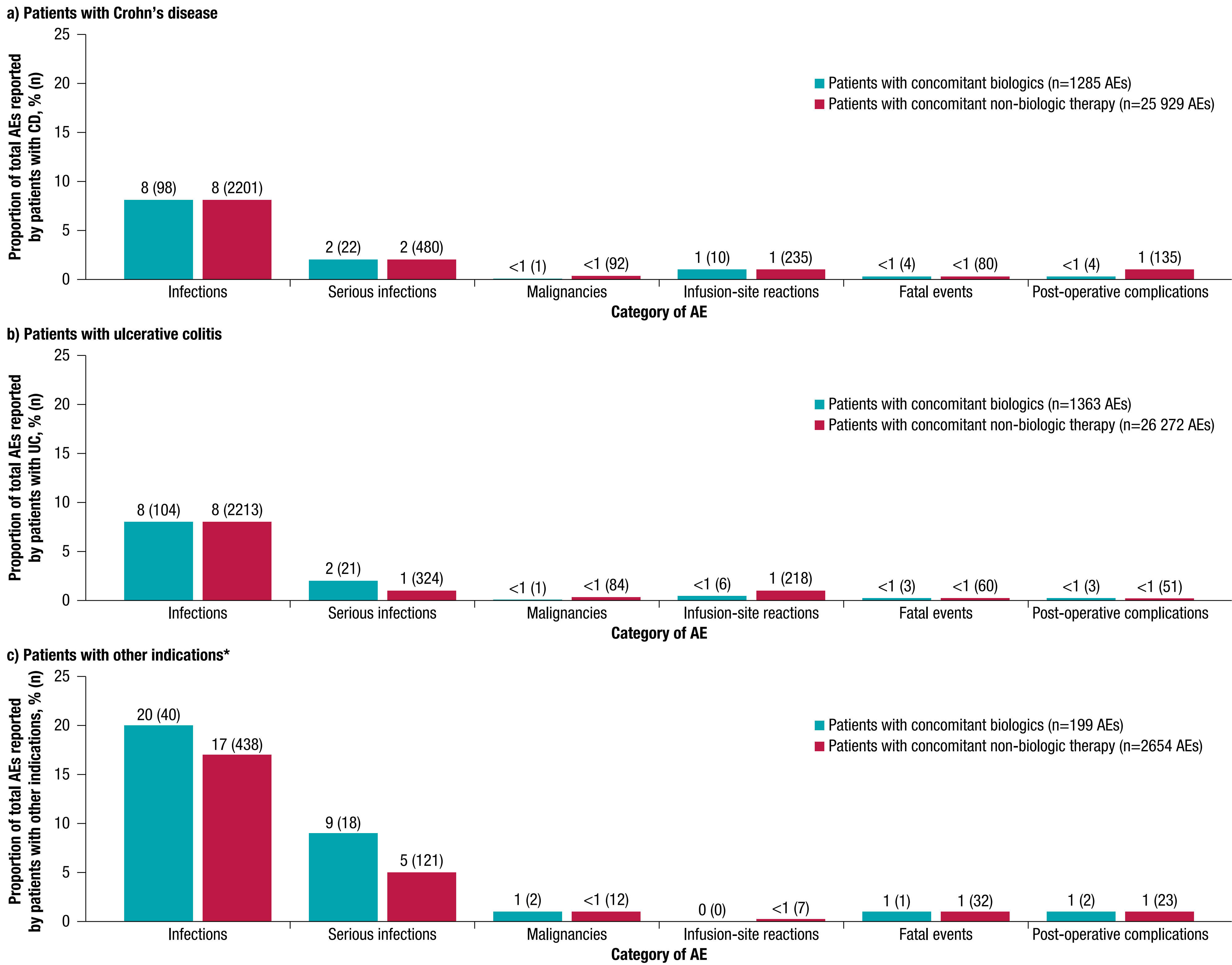
Overview of patient characteristics and total adverse events

- In the context of an estimated 208 050 patient-years of vedolizumab exposure in the post-marketing setting, 32 752 patients reported AEs, with 80 218 AEs reported in total.
- There were 1112 patients (3% of all AE-reporting patients; 460 with CD, 543 with UC and 109 with 'other' indications, which included unspecified inflammatory bowel disease, off-label use or an unreported indication) receiving vedolizumab with concomitant biologics who reported AEs.
 - These patients reported 2847 AEs (4% of all AEs; 1285 in patients with CD, 1363 in those with UC).
- There were 20 201 patients (62% of all AE-reporting patients; 8861 with CD, 10 113 with UC and 1227 with other indications) receiving vedolizumab concomitantly with non-biologics who reported AEs.
 - These patients reported a total of 54 855 AEs (68% of all AEs; 25 929 in patients with CD and 26 272 in patients with UC).
- The remaining 11 439 patients reporting AEs (35% of all AE-reporting patients; 4870 with CD, 3386 with UC and 3183 with other indications) did not report receiving any form of concomitant treatment (data for these patients were not analysed here).
 - These patients reported a total of 22 516 AEs (28% of all AEs; 46% in patients with CD and 29% in patients with UC).
- Proportions of patients in each age group and sex were similar in those with concomitant biologic use and those with concomitant non-biologic therapy.
 - Most patients were aged 18–64 years (87% of patients receiving concomitant biologics, 78% of those receiving concomitant non-biologic therapy), while a total of 53% and 56% of patients were female, respectively (Table 1).
- Of the patients receiving concomitant biologics, the majority of patients for each indication received anti-TNF α therapy (Table 1).
- Similar proportions of patients receiving concomitant treatment both with and without biologics reported use of concomitant corticosteroids (44% vs 49%, respectively) and/or concomitant non-biologic immunomodulator use (30% vs 24%, respectively).

Adverse events in patients receiving concomitant biologics and concomitant non-biologic therapy

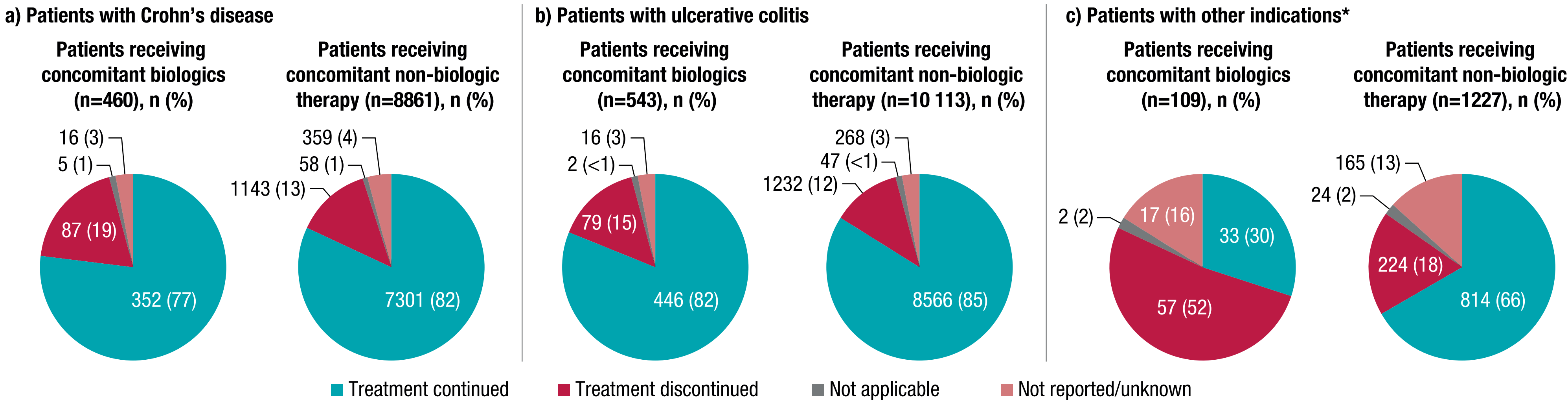
- The proportions of AEs reported in each category of AE were similar for patients receiving vedolizumab with concomitant biologic therapy and with concomitant medications that did not include other biologics.
 - In patients receiving concomitant biologics, 1003 patients with CD or UC reported a total of 2648 AEs:
 - there were 202 infections (8% of AEs reported in this patient group), 43 (21%) of which were serious (Figure 1)
 - there were 7 post-operative complications (<1% of AEs), 16 infusion-site reactions (1%) and 2 malignancies (<1%)
 - there were 7 AEs reported (<1% of AEs) that resulted in a fatal outcome in 5 patients (4 CD, 1 UC; Figure 1).
 - In patients receiving concomitant non-biologic therapy, 18 974 patients with CD or UC reported a total of 52 201 AEs:
 - There were 4414 infections (8% of AEs), of which 804 (18%) were serious (Figure 1).
 - Also reported were 186 post-operative complications (<1% of AEs), 453 infusion-site reactions (1%), 176 malignancies (<1%) and 140 fatal AEs (<1% of AEs; 80 CD, 60 UC; Figure 1).
 - The most frequently reported serious infections in patients with concomitant biologics were intestinal abscess, anal abscess and pneumonia (two events each [9% of serious infections for indication]) in CD and *Clostridium difficile* infection/colitis (three events [14%]), pneumonia and cytomegaloviral infection/colitis (two events each [10%]) in UC.

Figure 1. The proportions of AEs in each AE category reported in patients receiving vedolizumab with concomitant biologics and with concomitant non-biologic therapy



*Including patients with unspecified inflammatory bowel disease, off-label use and unreported indications
Malignancy events in both patient groups excluded colon adenomas, benign events and non-melanoma skin cancer, as well as malignancies in patients for which the reported onset date of the malignancy was before initiation of vedolizumab therapy. Of the four malignancies in patients with concomitant biologics, there was one lower GI malignancy (Crohn's disease), two haematological malignancies (one ulcerative colitis, one other indication*) and one neuroendocrine malignancy (one other indication)
Of the fatal events in patients with concomitant biologics, three reports contained the term 'death' with no further detail (all in patients with Crohn's disease), one event was listed as adenocarcinoma (Crohn's disease), one was leukaemia (off-label use for graft-versus-host disease) and one patient with ulcerative colitis had three events recorded as fatal (ulcerative colitis, multiple organ dysfunction syndrome and drug ineffective)
AE, adverse event; CD, Crohn's disease; GI, gastrointestinal; UC, ulcerative colitis

Figure 2. Vedolizumab continuation in patients receiving vedolizumab with concomitant biologics and with concomitant non-biologic therapy and reporting AEs



*Including patients with unspecified inflammatory bowel disease, off-label use and unreported indications
'Not applicable' comprises reports of fatal events (where the patient had died), reports where vedolizumab had been stopped for another or unspecified reason prior to the event, reports for which the source documentation stated that action taken was 'not applicable' with no further detail, and to reports relating to neonates (where exposure to vedolizumab occurred via the mother)

- The proportion of AEs reported in each category of AE was similar for patients with CD or UC.
 - In patients receiving vedolizumab for other indications, the proportion of AEs reported as infections and serious infections was higher than that reported in patients with CD or UC, and was slightly higher for patients receiving concomitant biologics compared with those receiving concomitant non-biologic therapy (Figure 1).

Continuation of vedolizumab treatment

- Despite experiencing an AE, most patients with CD or UC receiving concomitant biologics continued vedolizumab therapy (352 patients [77%] and 446 patients [82%], respectively; Figure 2).
- Similarly, 7301 patients with CD (82%) and 8566 patients with UC (85%) receiving concomitant non-biologic therapy also continued treatment with vedolizumab, despite reporting an AE (Figure 2).

Table 1. Characteristics of patients reporting AEs while receiving vedolizumab with concomitant biologics and with concomitant non-biologic therapy

Characteristic, n (%)	Patients reporting AEs while receiving vedolizumab with concomitant biologic treatment			Patients reporting AEs while receiving vedolizumab with concomitant non-biologic treatment		
	Crohn's disease n=460	Ulcerative colitis n=543	Other indications* n=109	Crohn's disease n=8861	Ulcerative colitis n=10 113	Other indications* n=1227
Sex						
Female	279 (61)	240 (44)	69 (63)	5499 (62)	5130 (51)	723 (59)
Male	178 (39)	301 (55)	35 (32)	3341 (38)	4954 (49)	473 (39)
Not reported	3 (1)	2 (<1)	5 (5)	21 (<1)	29 (<1)	31 (3)
Age, years						
<18 years [†]	7 (2)	6 (1)	2 (2)	118 (1)	231 (2)	28 (2)
18–64 years	406 (88)	481 (89)	75 (69)	7089 (80)	8025 (79)	653 (53)
≥65 years	39 (8)	48 (9)	4 (4)	1484 (17)	1702 (17)	195 (16)
Not reported	8 (2)	8 (1)	28 (26)	170 (2)	155 (2)	351 (29)
Concomitant biologics [‡]						
Concomitant anti-TNF α therapy	339 (74)	520 (96)	73 (67)	—	—	—
Other concomitant biologic therapy	117 (25)	22 (4)	34 (31)	—	—	—
Concomitant anti-TNF α and other biologics	4 (1)	1 (<1)	2 (2)	—	—	—
Other concomitant immunosuppressant						
Yes	133 (29)	167 (31)	32 (29)	2110 (24)	2399 (24)	276 (22)
No	327 (71)	376 (69)	77 (71)	6751 (76)	7714 (76)	951 (78)
Concomitant corticosteroid						
Yes	180 (39)	261 (48)	49 (45)	3763 (42)	5697 (56)	432 (35)
No	280 (61)	282 (52)	60 (55)	5098 (58)	4416 (44)	795 (65)

*Including patients with unspecified inflammatory bowel disease, off-label use and unreported indications
[†]Vedolizumab is not approved for use in patients <18 years of age
[‡]Receipt of vedolizumab therapy concomitantly with other biologics is not recommended in the vedolizumab prescribing information^{1,2}
AE, adverse event; TNF α , tumour necrosis factor alpha

Conclusions

- This analysis provides comparative information on the safety of vedolizumab when used with concomitant biologics compared with concomitant non-biologic therapy in the real-world setting.
- The safety profile of vedolizumab appears to be similar in patients with CD or UC receiving vedolizumab with concomitant biologics or concomitant non-biologic therapy, with no evidence of any substantial differences in the proportion of the different AEs of interest between patient groups.
- Limitations of post-marketing safety reports should be considered when interpreting these results, including:
 - the duration of vedolizumab use concomitantly with other biologics was not included in reports
 - the voluntary nature of AE reporting
 - the increased likelihood of reporting of more serious versus less serious AEs
 - incomplete details in post-marketing reports making causal associations between drug exposure and AEs difficult to assess.
- In addition, limitations pertaining to these particular data include the following:
 - The numbers of AEs reported in each AE category by patients receiving vedolizumab with concomitant biologics were small
 - The number of patients receiving vedolizumab with concomitant biologics reporting AEs was much lower than the number of patients reporting AEs while receiving vedolizumab with concomitant non-biologic therapy.

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Disclosures

- Russell D Cohen** has received speakers' bureau honoraria from AbbVie and Takeda; has served as a consultant, adviser or member of scientific advisory boards for AbbVie, Celgene, Eli Lilly, Hospira, Janssen, Pfizer, Sandoz, Takeda and UCB; has received grants or research support from AstraZeneca, Celgene, Gilead, Medimmune, Mesoblast Ltd, Osiris Therapeutics, Pfizer, Receptos, RedHill Biopharma, Sanofi and UCB.
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