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Vedolizumab Use is not Associated with Increased Malignancy Incidence: GEMINI Long-Term Safety Study Results and Post-Marketing Data

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Background

- Inflammatory bowel disease (IBD) and the use of immunomodulators for its treatment, including thiopurines[1] and biologics (such as infliximab[2] and other anti-tumour necrosis factor alpha [TNFα] antibodies), have been associated with increased risk of malignancy.[3–5]
- Vedolizumab (ENTYVIO®) is a gut-selective, 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.[6,7]
- An integrated analysis of data from six clinical trials found that vedolizumab was not associated with an increased rate of malignancy compared with that usually observed in a population with IBD.[8]
- This analysis provides further evidence on the incidence of malignancy in patients with CD or UC receiving vedolizumab, using data from the GEMINI Long-Term Safety (LTS) study (NCT00790933) and post-marketing data from the Vedolizumab Global Safety Database.

Methods

Data from the GEMINI LTS Study

- We describe data on malignancies gathered in the LTS study between 22 May 2009 and 19 May 2018.
- Relevant adverse events (AEs) were identified using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 System Organ Class term "neoplasms benign, malignant, and unspecified (including cysts and polyps)".
  - The following events were not included: benign neoplasms, basal cell carcinomas, colon adenomas, haemangioma, neurilemmoma, non-melanoma skin cancers and malignancies with diagnoses reported prior to initiation of vedolizumab treatment.

Comparison of Observed Versus Expected Malignancy Events

- The number of patients with a malignancy observed in the LTS study was indirectly standardized against the number expected, using age- and sex-specific rates of malignancy in patients with IBD from a large, de-identified insurance claims database: Optum's Clinformatics Data Mart (CDM).
  - To avoid misclassifying prevalent malignancy prior to vedolizumab exposure in the LTS study, events observed within 1 year after the first dose of vedolizumab were excluded; the corresponding follow-up time was also not used in the analysis.
- Time-adjusted rates of malignancy in the CDM database (reference population) were calculated for each age group and sex by dividing the numbers of events in each group by the total number of patient-years.
  - These values were then used to calculate the time-adjusted expected numbers of malignancies for each anatomical site for the LTS study population.

Post-marketing Data from the Vedolizumab Global Safety Database

- All post-marketing AE reports received by the licence holder, Takeda Pharmaceutical Company Ltd, since first approval of vedolizumab (20 May 2014) are held in the Vedolizumab Global Safety Database. Sources of these reports include:
  - spontaneous reports from patients, healthcare professionals and regulatory authorities
  - solicited reports from patient-support and market-research programmes
  - reports extracted from the literature.
- All post-marketing reports concerning malignancies received between vedolizumab first approval and 19 May 2018 were identified using the MedDRA version 21.0 System Organ Class term "neoplasms benign, malignant, and unspecified (including cysts and polyps)" and then grouped according to anatomical site.
  - For consistency with data from the LTS study, benign neoplasms, colon adenomas, non-melanoma skin cancers and all malignancies with diagnoses reported prior to the start of vedolizumab treatment were excluded; events reported within the first year of vedolizumab exposure were included because 126 (42%) of the malignancies reported did not contain information on the malignancy diagnosis date relative to vedolizumab therapy initiation.

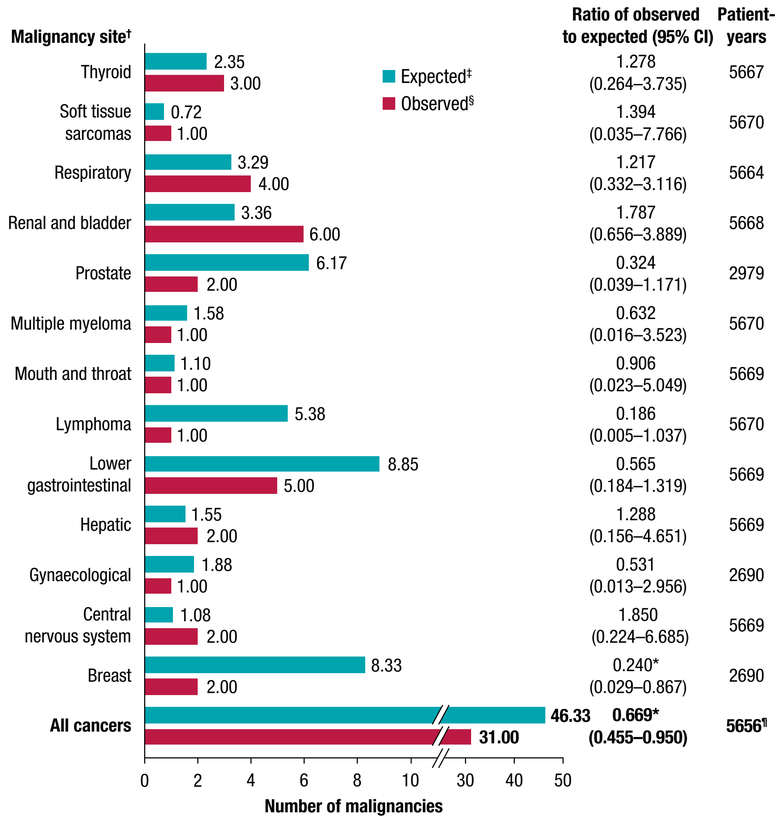
Results

Data from the GEMINI LTS Study

Overview of malignancies and baseline characteristics

- There were 2243 patients enrolled in the LTS study, of which 1785 had at least 1 year of exposure to vedolizumab.
  - Baseline characteristics of these 1785 patients are listed in Table 1.
- In 5670 patient-years of vedolizumab exposure, 31 patients (17 with CD, 14 with UC) experienced malignancies. Of these, 14 (45%) were female and the mean (standard deviation) age was 51.2 (10.5) years (Table 1).

Figure 1. Indirect standardization of the numbers of patients with malignancy events in the GEMINI LTS study by anatomical site



*p<0.05. †Malignancies were identified using Medical Dictionary for Regulatory Activities version 20.0 System Organ Class term "neoplasms benign, malignant, and unspecified (including cysts and polyps)". Benign neoplasms, basal cell carcinoma, colon adenoma, haemangioma, neurilemmoma, all non-melanoma skin cancers, and malignancies with diagnoses reported before, or within 1 year after, the start of vedolizumab treatment (i.e. those in patients who received placebo in the lead-in studies) were excluded. The corresponding follow-up time for excluded malignancies was not used in the analysis. ‡The expected number of patients with malignancies in the GEMINI LTS study was estimated by indirectly standardizing against age- and sex-specific malignancy rates in patients with inflammatory bowel disease in Optum's Clinformatics Data Mart database. §Patients with more than one malignancy at a single site were counted only once. ¶Survival time was measured up to time of failure or end of study follow-up. As a result, the total number of patient-years is reduced vs values of each site individually
CI, confidence interval; LTS, Long-Term Safety

- Prior use of anti-TNFα therapy was reported by 65% of patients with CD and 57% of patients with UC experiencing a malignancy (Table 1).
- Sites with malignancies occurring in the most patients were renal and bladder (3 CD, 3 UC), lower gastrointestinal (2 CD, 3 UC [including one patient with UC with two events]), and respiratory (1 CD, 3 UC).
  - Malignancies at all other sites were observed in three or fewer patients (Figure 1).

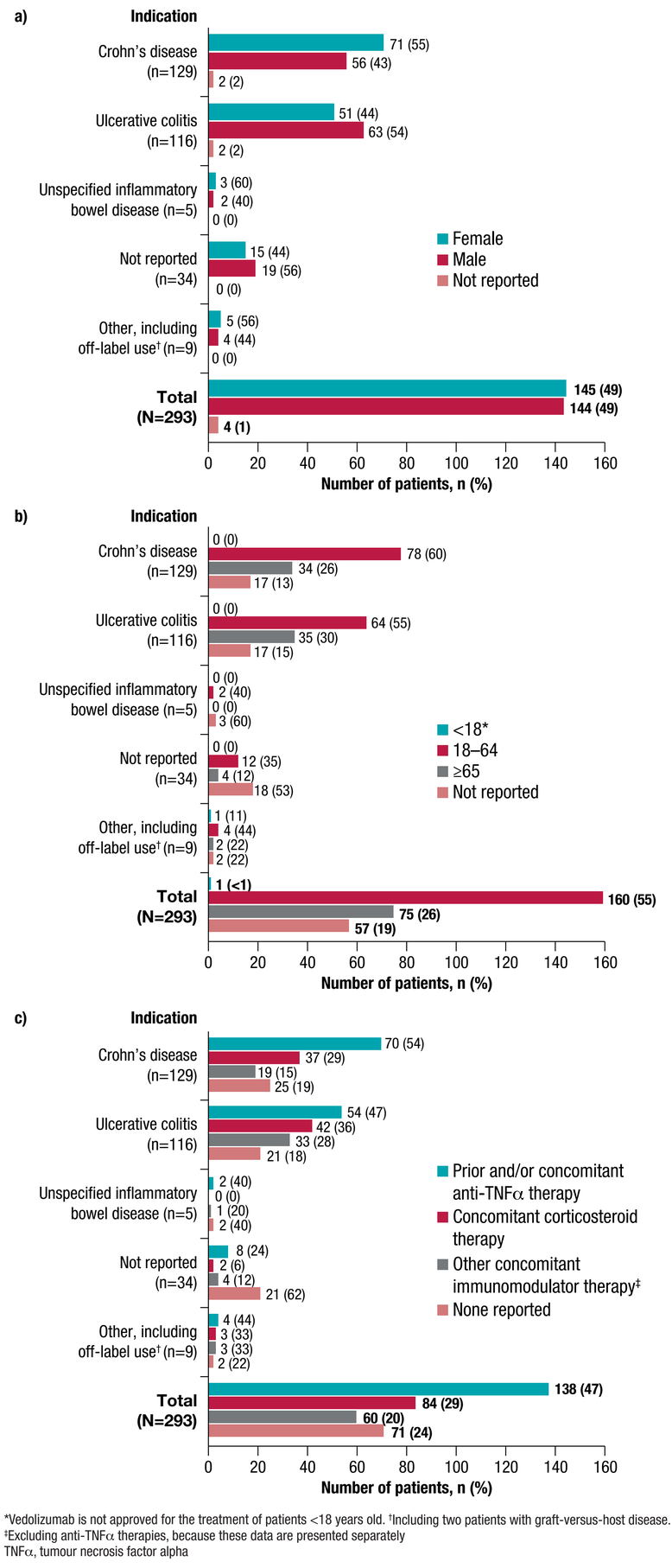
Comparison with the CDM database of observed versus expected malignancies

- The overall number of patients with malignancies observed across all sites in the LTS study was significantly lower than the expected number, estimated using an age- and sex-adjusted reference population (31 vs 46; p=0.0222), corresponding to a ratio of total observed to total expected events of 0.67 (95% confidence interval [CI], 0.46–0.95; Figure 1).
- With respect to the malignancies observed in these patients at individual anatomical sites, observed numbers of malignancies at each site did not differ significantly from the expected number (p>0.05), except for in the breast, where the observed number was lower than expected (2 vs 8; ratio, 0.24; 95% CI, 0.03–0.87; p=0.0212; Figure 1).

Post-marketing Data from the Vedolizumab Global Safety Database

- In the post-marketing setting, 299 malignancies were reported in 293 patients in the context of 208 050 patient-years of exposure.
  - Six patients reported a malignancy at more than one site.
- Of the 293 patients with reported malignancies, 145 (49%) were female and 160 (55%) were aged 18–64 years (Figure 2).
  - With respect to indication, 129 patients (44%) had CD and 116 (40%) had UC.
- Prior and/or concomitant anti-TNFα therapy, concomitant corticosteroid use, and/or other concomitant immunomodulatory therapies were reported in 47%, 29% and 20% of patients, respectively (Figure 2).

Figure 2. a) sex, b) age (years) and c) use of prior and/or concomitant therapy of patients reporting malignancies while receiving vedolizumab for different indications in the post-marketing setting



*Vedolizumab is not approved for the treatment of patients <18 years old. †Including two patients with graft-versus-host disease. ‡Excluding anti-TNFα therapies, because these data are presented separately
TNFα, tumour necrosis factor alpha

- Across all indications (including unspecified IBD, off-label use and unreported indications), the most common malignancies were lower gastrointestinal (59 events [20%]) and lymphoma (33 events [11%]; Table 2).
- Numbers of reported malignancies were similar whether patients were receiving vedolizumab for CD (134) or UC (117).

Table 1. Baseline characteristics of patients in the GEMINI LTS study

Characteristic	Patients with at least 1 year of vedolizumab exposure			Patients experiencing a malignancy		
	Crohn's disease (n=1034)	Ulcerative colitis (n=751)	Total (N=1785)	Crohn's disease (n=17)	Ulcerative colitis (n=14)	Total (N=31)
Sex, female, n (%)	549 (53)	331 (44)	880 (49)	9 (53)	5 (36)	14 (45)
Age, years						
Mean (SD)	38.3 (12.64)	41.3 (13.20)	39.5 (12.96)	51.8 (8.50)	50.5 (12.82)	51.2 (10.50)
Median	36.8	40.8	38.1	52.7	49.7	52.1
Race, n (%)						
Asian	65 (6)	95 (13)	160 (9)	0 (0)	1 (7)	1 (3)
White	937 (91)	632 (84)	1569 (88)	17 (100)	12 (86)	29 (94)
Other	32 (3)	24 (3)	56 (3)	0 (0)	1 (7)	1 (3)
Duration of disease, years						
Mean (SD)	10.0 (8.42)	8.0 (6.79)	9.2 (7.83)	12.9 (10.36)	10.5 (9.78)	11.8 (10.01)
Median	7.8	5.8	6.8	8.9	7.0	7.8
Baseline disease activity, mean (SD)						
Partial Mayo score	–	3.8 (2.91)	–	–	3.9 (3.34)	–
Harvey–Bradshaw Index score	7.3 (4.89)	–	–	8.2 (4.48)	–	–
Smoking history, n (%)						
Current smoker	275 (27)	39 (5)	314 (18)	7 (41)	0 (0)	7 (23)
Former smoker	254 (25)	218 (29)	472 (26)	4 (24)	5 (36)	9 (29)
Never smoked	499 (48)	466 (62)	965 (54)	6 (35)	9 (64)	15 (48)
Unknown/missing data	6 (1)	28 (4)	34 (2)	0 (0)	0 (0)	0 (0)
Treatment history, n (%)						
Prior anti-TNFα therapy	640 (62)	321 (43)	961 (54)	11 (65)	8 (57)	19 (61)
Any prior anti-TNFα therapy failure*	598 (58)	290 (39)	888 (50)	10 (59)	7 (50)	17 (55)
Concomitant immunomodulatory therapy	317 (31)	204 (27)	521 (29)	8 (47)	4 (29)	12 (39)
Concomitant corticosteroid therapy	452 (44)	314 (42)	766 (43)	7 (41)	8 (57)	15 (48)

*Patients reporting any prior anti-TNFα therapy failure are a subset of those reporting prior anti-TNFα therapy
LTS, Long-Term Safety; SD, standard deviation; TNFα, tumour necrosis factor alpha

- Despite limitations of post-marketing safety reports, such as voluntary reporting meaning that all malignancy events may not be captured, the numbers of malignancies reported with vedolizumab appear low.
- These data show no evidence of any increase in incidence of malignancy in patients with IBD receiving vedolizumab compared with what would be expected in patients with IBD.
- Additional data on the incidence of malignancy with vedolizumab use from the post-authorization safety study and continued post-marketing surveillance will continue to be evaluated.

Table 2. Numbers of reported malignancy events by anatomical site and indication in the post-marketing setting

Malignancy*	Indication, n (%)					
	Crohn's disease (n=134)	Ulcerative colitis (n=117)	Unspecified inflammatory bowel disease (n=5)	Not reported (n=34)	Other, including off-label use (n=9)	Total (N=299)
Lower gastrointestinal	21 (16)	34 (29)	2 (40)	2 (6)	0 (0)	59 (20)
Lymphoma	11 (8)	14 (12)	1 (20)	5 (15)	2 (22)	33 (11)
Breast	11 (8)	10 (9)	0 (0)	2 (6)	1 (11)	24 (8)
Renal and bladder	18 (13)	4 (3)	0 (0)	2 (6)	0 (0)	24 (8)
Respiratory	7 (5)	12 (10)	0 (0)	4 (12)	0 (0)	23 (8)
Skin (unspecified/other)	12 (9)	5 (4)	0 (0)	3 (9)	0 (0)	20 (7)
Unspecified malignant neoplasm	9 (7)	3 (3)	1 (20)	4 (12)	1 (11)	18 (6)
Gallbladder, bile duct and pancreatic	10 (7)	5 (4)	0 (0)	0 (0)	0 (0)	15 (5)
Haematological	6 (4)	5 (4)	0 (0)	0 (0)	3† (33)	14 (5)
Ear, nose and throat	6 (4)	4 (3)	0 (0)	1 (3)	0 (0)	11 (4)
Thyroid	4 (3)	3 (3)	1 (20)	2 (6)	0 (0)	10 (3)
Prostate	2 (1)	6 (5)	0 (0)	1 (3)	0 (0)	9 (3)
Skin (melanoma)	4 (3)	1 (1)	0 (0)	3 (9)	1 (11)	9 (3)
Central nervous system	4 (3)	3 (3)	0 (0)	1 (3)	0 (0)	8 (3)
Neuroendocrine	2 (1)	3 (3)	0 (0)	0 (0)	1 (11)	6 (2)
Gynaecological	2 (1)	3 (3)	0 (0)	0 (0)	0 (0)	5 (2)
Hepatic	3 (2)	0 (0)	0 (0)	2 (6)	0 (0)	5 (2)
Oesophageal and gastric	2 (1)	0 (0)	0 (0)	2 (6)	0 (0)	4 (1)
Bone	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)
Unspecified gastrointestinal neoplasm	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)

Percentages at individual sites are calculated using the total number of malignancies reported in patients taking vedolizumab for the corresponding indication
*Malignancies were identified using the Medical Dictionary for Regulatory Activities version 21.0 System Organ Class term "neoplasms benign, malignant, and unspecified (including cysts and polyps)" and then grouped according to anatomical site. Benign neoplasms, colon adenomas, non-melanoma skin cancers and all malignancies with diagnoses reported before the start of vedolizumab treatment were excluded. †Including one event each for two patients with graft-versus-host disease

Conclusions

- In the GEMINI LTS study of patients treated with vedolizumab, the total number of observed malignancies across anatomical sites was lower than expected after age- and sex-standardization against patients with IBD in the CDM database.
  - The significance of malignancy rates at specific sites should not be overinterpreted because of small numbers.
- Despite limitations of post-marketing safety reports, such as voluntary reporting meaning that all malignancy events may not be captured, the numbers of malignancies reported with vedolizumab appear low.
- These data show no evidence of any increase in incidence of malignancy in patients with IBD receiving vedolizumab compared with what would be expected in patients with IBD.
- Additional data on the incidence of malignancy with vedolizumab use from the post-authorization safety study and continued post-marketing surveillance will continue to be evaluated.

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Disclosures

- **T Card** is employed by the University of Nottingham; neither he nor the University received any payment financial or in kind related to this work. He has no active conflicts of interest to declare but was formerly married to an employee of Takeda.
- **R Ungaro** has served as a consultant and/or advisory board member for Janssen, Pfizer and Takeda. He has received research support from AbbVie and Pfizer.
- **F Bhayat**, **A Blake** and **G Hantsbarger** are employed by Takeda Pharmaceutical International Co.
- **S Travis** is employed by Oxford University Hospitals NHS Foundation Trust and the University of Oxford. He has received grants or research support from AbbVie, Bühlmann, International Organization for the Study of Inflammatory Bowel Diseases, Lilly, Mediadd, Norman Collisson Foundation, UCB and Vifor; consulting fees from AbbVie, Ajinomoto, Almirall, Amgen, Asahi, Atlantic, Bioclinica, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Calcico, Celgene, ChemoCentryx, Cosmo, Covance, Enterome, Falk, Ferring, Genentech, Gilead, Giuliani SpA, GlaxoSmithKline, Glenmark, Grünenthal, Immunocore, Immunometabolism, Istesso, Janssen, Lexicon, Lilly, Medarex, Merck, MSD, Napp, Neovacs, Novartis, Novo Nordisk, NPS Pharmaceuticals, Ocera, Otsuka, Pfizer, Pharm-Olam, Phillips, Proximagen, Quintiles, Receptos, Robarts, Roche, Sandoz, Shire, Sigmoid Pharma, Takeda, Theravance, TiGenix, Topivert, UCB, Vertex, VHsquared, Vifor, Warner Chilcott and Zeria; and speaker fees from AbbVie, Amgen, Biogen, Ferring, Sandoz, Shire, Takeda and Zeria. He has no stocks or share options.

Acknowledgements

- This work was supported in part by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.
- Medical writing assistance was provided by Fraser Harris of Oxford PharmaGenesis and sponsored by Takeda Pharmaceutical Company Ltd.

Presented at the 14th Congress of European Crohn's and Colitis Organisation • March 6–9, 2019 • Copenhagen, Denmark