# Post-marketing Experience of Vedolizumab in Inflammatory Bowel Disease: Analysis of Pneumonia and Other Respiratory Tract Infections

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## 1. Background

- The annual incidence of pneumonia has been reported as 13.8/1000 in patients with IBD compared with 7.6/1000 in healthy individuals (incidence rate ratio 1.82; 95% CI: 1.75–1.88)[1]
- Vedolizumab (ENTYVIO®) is a humanized, monoclonal antibody that selectively targets the $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes, with non-gut-homing T-lymphocytes remaining unaffected[2,3]
- Although respiratory tract infections (RTIs) have been reported with vedolizumab,[4] its gut selectivity may reduce the risk of RTIs compared with therapies that produce systemic immunosuppression (e.g. anti-tumor necrosis factor-alpha [TNFα] agents)[5]
- Vedolizumab is licensed in over 50 countries to treat adults with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD),[4] and has been incorporated into the latest European Crohn's and Colitis Organisation guidelines for CD[6]
- Here, we describe pneumonia and other RTIs reported with vedolizumab therapy in the post-marketing setting

## 2. Methods

- A review of safety data from the vedolizumab post-marketing Global Safety Database was conducted (between launch [May 2014] and May 19, 2016)
  - Estimated vedolizumab exposure was ~46,978 patient-years (PY)
- Reports of lower RTIs (LRTIs) and upper RTIs (URTIs) were identified using the following MedDRA v19.0 High Level Terms: 'Lower Respiratory Tract (LRT) and lung infections', 'LRTIs not elsewhere classified (NEC)', 'URTIs', and 'URTIs (NEC)'

## 3. Results

- Patient demographics and clinical characteristics are presented in Table 1

### Table 1. Patient Demographics and Clinical Characteristics

| | LRTIs (N=106 patients) | URTIs (N=300 patients) |
|---|---|---|
| Female sex, n/N (%) | 66/105 (62.9)* | 173/279 (62.0)† |
| Age, mean (SD) years | 46.5 (16.5) | 43.0 (14.7) |
| Current/former smoker, n/N (%) | 6/10 (60.0)‡ | 5/20 (25.0)§ |
| Prior/concomitant anti-TNFα therapy, n/N (%) | 53/74 (71.6) | 180/239 (75.3) |
| Prior/concomitant IMM use, n/N (%) | 26/74 (35.1) | 180/239 (75.3) |
| No prior/concomitant medications reported, n (%) | 32 (30.2) | 61 (20.3) |
| Surgery ≤30 days prior to event onset reported, n (%) | 2 (1.9)¶ | 1 (0.3)¶ |

Data cut-off: May 19, 2016; N = the number of patients with available information (denominator). If N is not stated, the denominator is the total number of patients overall (LRTI, N=106; URTI, N=300)
*Sex was not reported in one patient
†Sex was not reported in 21 patients
‡Smoking history was not reported in 96 patients
§Smoking history was not reported in 280 patients
¶104 and 299 patients with LRTIs and URTIs, respectively, did not report having surgery within 30 days prior to event onset
IMM, immunomodulator; LRTI, lower respiratory tract infection; TNFα, tumor necrosis factor-alpha; URTI, upper respiratory tract infection

### Frequency and Seriousness of LRTIs

- During ~46,978 PY of vedolizumab therapy, a total of 108 LRTIs were reported in 106 patients (Table 2)
  - Most events were non-serious (68/108 events; 63.0%; Figure 1)
- Overall, pneumonia accounted for 54 events (n=34 serious; n=20 non-serious). This was equivalent to ~1 event/1000 PY of therapy
  - There were 4 fatal pneumonia events (Table 3)
- The second most commonly reported LRTI was bronchitis (n=1 serious; n=26 non-serious)

### Table 2. Frequency of LRTIs

| Reported AE | Serious events | Non-serious events |
|---|---|---|
| *Total LRTI events* | *40* | *68* |
| Pneumonia | 34 | 20 |
| Bronchitis* | 1 | 26 |
| LRTIs (not specified) | 2 | 20 |
| Lung infection | 2 | 2 |
| Lung abscess | 1 | 0 |

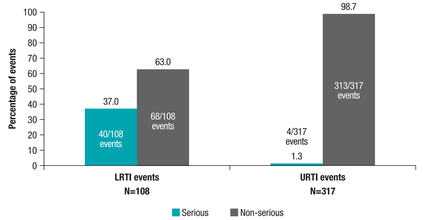
Data cut-off: May 19, 2016
*AE included in the vedolizumab prescribing information[4]
AE, adverse event; LRTI, lower respiratory tract infection

### Table 3. Fatal Events of Pneumonia

| Patient details | Cause of death | Concomitant and prior medications | Medical history |
|---|---|---|---|
| Male, 84 years, UC | • Pneumonia | • NR | • NR |
| Male, 71 years, UC | • Myocardial infarction<br>• Pulmonary embolism in the context of fatal pneumonia | • *Concomitant:* tamsulosin, prednisolone<br>• *Prior:* NR | • Coronary heart disease<br>• Cardiovascular disorder<br>• Hypertension<br>• Past pneumonia |
| Male, 53 years, CD | • Pneumonia | • NR | • COPD |
| Male, age NR, CD | • Septicemia<br>• Pneumonia | • *Concomitant:* calcium carbonate/ colecalciferol (Calcichew-D3), zinc sulfate (Solvezink), cyanocobalamin (Behepan), ferrous sulfate (Duroferon), folic acid (Folacin), betamethasone sodium phosphate (Betapred), fentanyl patches (Matrifen), parenteral nutrition (Nutriflex)<br>• *Prior:* NR | • Generalized illness |

Data cut-off: May 19, 2016
CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; NR, not reported; UC, ulcerative colitis

### Figure 1. Seriousness of RTIs




Data cut-off: May 19, 2016
~46,978 patient-years of vedolizumab therapy
LRTI, lower respiratory tract infection; RTI, respiratory tract infection; URTI, upper respiratory tract infection

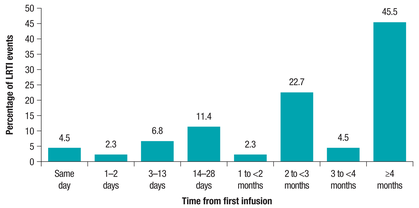
### Risk Factors for LRTIs, Including Pneumonia

- Known risk factors for pneumonia include smoking, recent surgery, older age (>65 years), and comorbidities, including immunosuppressive conditions[7,8]
- Smoking history was reported in a minority of patients with LRTIs (10/106) and URTIs (20/300) (Table 1)
- Information on prior surgery was reported for 7 patients with a pneumonia event; of these, two had undergone surgery ≤30 days prior to reporting pneumonia
- Of those experiencing an LRTI (and who had information regarding prior medication use), 53/74 (71.6%) reported prior/concomitant use of anti-TNFα therapy and 26/74 (35.1%) reported prior/concomitant immunomodulator use
  - Information regarding prior medication was not available in 32 patients

### LRTIs: Event Onset and Treatment Outcome

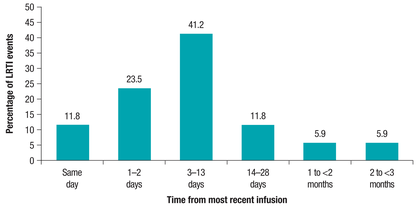
- From the 44 reports with available information, most LRTIs occurred ≥2 months after the first vedolizumab infusion (n=32/44 events; time to onset was not reported [NR] for n=64/108 events; Figure 2)
- From the 17 reports with available information, most (n=13/17; NR n=91/108 events) occurred ≤13 days after the most recent infusion of vedolizumab (Figure 3)
- Vedolizumab treatment was continued in most patients (n=61/89; NR n=17/106) who experienced an LRTI (Figure 4)

### Figure 2. Time to Onset of LRTI Events from the First Infusion (n=44 events)*



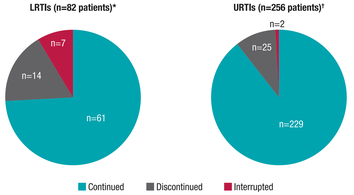

Data cut-off: May 19, 2016
*64 of 108 event reports did not have information available
LRTI, lower respiratory tract infection

### Figure 3. Time to Onset of LRTI Events from the Most Recent Infusion (n=17 events)*




Data cut-off: May 19, 2016
*91 of 108 event reports did not have information available
LRTI, lower respiratory tract infection

### Figure 4. Vedolizumab Treatment Status after an RTI Event




Data cut-off: May 19, 2016
*Total number of LRTI patients, N=106; vedolizumab treatment status after event NR in 17 patients; six patients died after the event (including four patients with fatal pneumonia [Table 3] and two patients that died as a result of events other than an LRTI); treatment was discontinued in one patient prior to LRTI onset
†Total number of URTI patients, N=300; vedolizumab treatment status after event NR in 43 patients; one patient died after the event as a result of an event other than the URTI
LRTI, lower respiratory tract infection; NR, not reported; URTI, upper respiratory tract infection

### Frequency and Seriousness of URTIs

- A total of 4 serious and 313 non-serious URTIs were reported in 300 patients (Table 4; Figure 1)
  - There were no fatal URTIs
- Nasopharyngitis was found to be a 'very common' adverse event (occurring in ≥1/10 patients) in the vedolizumab clinical trials[4] and, not unexpectedly, was the most frequently reported URTI (n=201/317 events reported from >46,000 PY of therapy)
  - Sinusitis and URTIs (not specified) were the next most frequently reported events (Table 4)

### Table 4. Frequency of URTIs

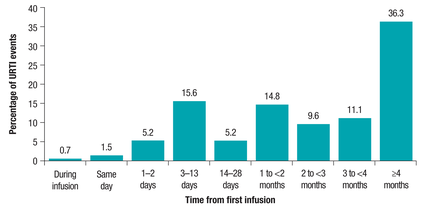
| Reported AE | Serious events | Non-serious events |
|---|---|---|
| *Total URTI events* | *4* | *313* |
| Nasopharyngitis* | 1 | 200 |
| Sinusitis* | 2 | 60 |
| URTIs* (not specified) | 0 | 22 |
| Pharyngitis | 1 | 14 |
| Rhinitis | 0 | 6 |
| Tonsillitis | 0 | 5 |
| Laryngitis | 0 | 5 |
| Croup | 0 | 1 |

Data cut-off: May 19, 2016
*AEs included in the vedolizumab prescribing information[4]
AE, adverse event; URTI, upper respiratory tract infection

### URTIs: Event Onset and Treatment Outcome

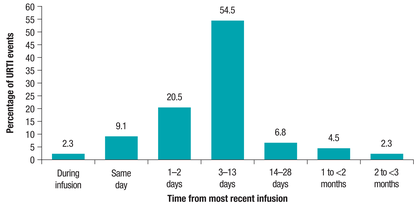
- From the 135 reports with available information, most URTIs occurred ≥2 months after the first vedolizumab infusion (n=77/135 events; NR n=182/317 events; Figure 5) and ≤13 days after the most recent infusion (n=38/44 events; NR n=273/317 events; Figure 6)
- Vedolizumab treatment was continued in most patients (n=229/257; NR n=43/300) who experienced a URTI (Figure 4)

### Figure 5. Time to Onset of URTI Events from First Infusion (n=135 events)*




Data cut-off: May 19, 2016
*182 of 317 event reports did not have information available
URTI, upper respiratory tract infection

### Figure 6. Time to Onset of URTI Events from the Most Recent Infusion (n=44 events)*




Data cut-off: May 19, 2016
*273 of 317 event reports did not have information available
URTI, upper respiratory tract infection

## 4. Conclusions

- **LRTIs (including pneumonia) were infrequently reported in real-life clinical practice**
- **The most frequently reported LRTI was pneumonia, which is likely to be a reflection of reporting bias of more serious events compared with non-serious events in the post-marketing setting**
- **Of the 106 patients with an LRTI from ~46,978 PY of therapy, 34 serious and 20 non-serious events of pneumonia were observed (equivalent to ~1 event/1000 PY of therapy)**
- **Vedolizumab treatment was continued after the event in over half of LRTI reports (including pneumonia)**
- **The observation that nasopharyngitis was the most commonly reported URTI is not unexpected, and is in line with findings from vedolizumab clinical trials[4,9]**
  - **Nasopharyngitis is also commonly reported with anti-TNFα treatment[10] and in the general population**
- **No new trends were identified in the characterization of RTIs from post-marketing experience with vedolizumab**
- **Limitations to consider when interpreting these data are those associated with post-marketing safety reporting, such as the voluntary nature of reporting, the inconsistent level of detail regarding patient history (including surgery and smoking), the timing of prior medication, and the resulting difficulty in establishing a causal relationship between drug and event**
- **Active pharmacovigilance will be maintained and, together with ongoing observational studies, will increase our understanding of RTIs with vedolizumab use**

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## Acknowledgments

This study was supported by Takeda Pharmaceutical Company Ltd. Medical writing support was provided by Chameleon Communications International Ltd, UK (a Healthcare Consultancy Group Company) and sponsored by Takeda Pharmaceutical Company Ltd. Analytical support was provided by Kelly Williams, formerly of Takeda Development Center Americas, USA.

## Disclosures

- Fatima Bhayat: employee of Takeda Development Centre Europe Ltd
- Aimee Blake: employee of Takeda Development Centre Europe Ltd
- Simon P. Travis: employee of Oxford University Hospitals NHS Foundation Trust and the University of Oxford; has received grants/research support from AbbVie, IOIBD, Lilly, Norman Collison Foundation, UCB, and Vifor; consulting fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, Cosmo, Ferring, Giuliani SpA, GlaxoSmithKline, Janssen, Lilly, MSD, Neovacs, Norman Collison Foundation, Novartis, Novo Nordisk, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Shire, Sigmoid Pharma, Takeda, Topivert, UCB, VHsquared, and Vifor; speaker fees from AbbVie, Amgen, Biogen, Ferring, and Takeda