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Incidence of Pneumonia and Other Respiratory Tract Infections with Vedolizumab Treatment for Inflammatory Bowel Disease: Clinical Trial Experience

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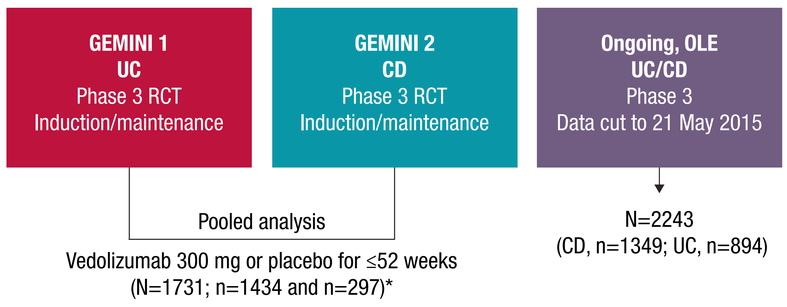
Background

- Anti-tumour necrosis factor-alpha (TNFα) agents have revolutionised the treatment of autoimmune diseases, including ulcerative colitis (UC) and Crohn's disease (CD); however, concerns remain regarding the safety of these agents[1]
- Because of their systemic immunosuppressive effects, patients treated with anti-TNFα agents are at increased risk of infections, including respiratory tract infections (RTIs) such as pneumonia[2–4]
- Vedolizumab (ENTYVIO®), approved for the treatment of adults with moderately to severely active UC or CD, is a humanised monoclonal antibody that targets $\alpha_4\beta_7$ integrin and selectively blocks gut-specific lymphocyte trafficking[5,6]
- Although RTIs have been reported with vedolizumab,[5,6] its gut selectivity may reduce the risk of events of this type, including pneumonia, compared with therapies causing systemic immunosuppression (e.g. anti-TNFα agents)
- Here, we aim to quantify the incidence rates of pneumonia and other RTIs associated with vedolizumab treatment in the clinical trial setting

Methods

- A post hoc analysis of adverse events (AEs) from three studies (Figure 1):
  - GEMINI 1 and 2: phase 3 randomised, placebo-controlled trials designed to examine the efficacy and safety of vedolizumab (versus placebo) for ≤52 weeks[7,8]
  - GEMINI open-label extension (OLE): an ongoing, open-label safety extension assessing the long-term safety of vedolizumab. An interim data cut to 21 May 2015 was used; 2243 patients had been enrolled (1349 with CD; 894 with UC)[9–11]
    - Study population included patients who had previously participated in vedolizumab clinical studies (GEMINI 1, 2, 3 and a phase 2 extension study) and *de novo* patients[9–11]

Figure 1. Clinical Data Sources[7–11]



*N=1731 comprises combined vedolizumab and non-ITT ('true') placebo groups, respectively
CD, Crohn's disease; ITT, intention-to-treat; OLE, open label extension; RCT, randomised controlled trial; UC, ulcerative colitis

- Lower RTIs (LRTIs), including pneumonia, and upper RTIs (URTIs) were defined for AEs based on the Medical Dictionary for Regulatory Activities (MedDRA; version 14.0) High Level Terms (HLTs):
  - LRTIs: Lower Respiratory Tract and Lung Infections HLT
  - URTIs: Upper Respiratory Tract Infections HLT
- For each study and the pooled analysis of GEMINI 1 and 2, exposure-adjusted incidence rates (per 100 patient-years [PY]) were calculated for the incidence of any AE and any serious AE within the HLT, as well as for each individual MedDRA Preferred Term (PT) within the HLT
- A Cox proportional hazards model was used to identify predictors for the incidence of any LRTI or any URTI for the individual and pooled GEMINI 1 and 2 results

Results

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics are presented in Table 1

Table 1. Baseline Demographics and Disease Characteristics: GEMINI 1, 2 and OLE

Demographic/characteristic*	GEMINI 1 (N=769)	GEMINI 2 (N=962)	Pooled GEMINI 1 and 2 (N=1731)	GEMINI OLE (N=2243)
Age (years), mean (SD)	40.3 (13.0)	35.9 (12.1)	37.9 (12.7)	39.1 (13.2)
Female sex	313 (40.7)	514 (53.4)	827 (47.8)	1115 (49.7)
Baseline disease activity, mean score (SD)†	6.1 (1.6)	11.2 (3.8)	5.8 (1.7)	NA
Concomitant narcotic use	148 (19.2)	315 (32.7)	463 (26.7)	777 (34.6)
Concomitant corticosteroid use	409 (53.2)	488 (50.7)	897 (51.8)	1133 (50.5)
Concomitant immunomodulator use	257 (33.4)	321 (33.4)	578 (33.4)	618 (27.6)
On-study surgery	64 (8.3)	139 (14.4)	203 (11.7)	NA
Disease duration ≥7 years	267 (34.7)	483 (50.2)	750 (43.3)	1127 (50.2)
Prior use of anti-TNFα therapy	384 (49.9)	607 (63.1)	991 (57.3)	1313 (58.5)
Current smoker	47 (6.1)	250 (26.0)	297 (17.2)	406 (18.1)
Former smoker	254 (33.0)	219 (22.8)	473 (27.3)	591 (26.3)

Prior lung disease was not a specific exclusion criterion

*Data presented as n (%) unless stated otherwise

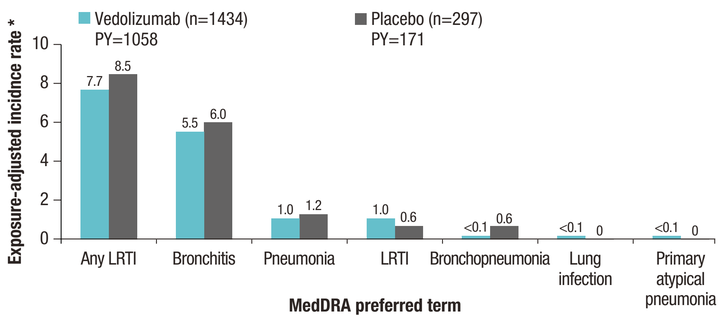
†Baseline disease activity scores based on partial Mayo Score for GEMINI 1 (UC), HBI score for GEMINI 2 (CD) and common index for pooled GEMINI 1 and 2. Common index ranged from 0 to 9 to allow the combination of baseline partial Mayo and HBI scores in the pooled analysis

CD, Crohn's disease; HBI, Harvey–Bradshaw Index; NA, not available; OLE, open-label extension; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis

Exposure-Adjusted Incidence Rates and Outcomes of LRTIs and URTIs

- In the pooled GEMINI 1 and 2 analysis, rates of LRTIs including pneumonia, bronchopneumonia and primary atypical pneumonia were similar in the vedolizumab and placebo groups (Figure 2)
- There was no increase in the OLE incidence rates of these events relative to those in the pooled GEMINI 1 and 2 analysis (Figures 2 and 3)
  - Bronchitis, which is listed as a common AE in the vedolizumab summary of product characteristics,[5] was the most frequently reported LRTI in both the vedolizumab and placebo groups in the GEMINI 1 and 2 population and in the OLE
- The incidence rate of URTIs was higher in patients receiving vedolizumab than in those on placebo (Table 2)
  - Nasopharyngitis and URTI (listed as very common and common AEs, respectively, in the vedolizumab summary of product characteristics[5]), were the most frequently reported URTIs in both the vedolizumab and placebo groups in the GEMINI 1 and 2 population and in the OLE
  - Sinusitis and pharyngitis are also reported as common AEs in the summary of product characteristics[5]

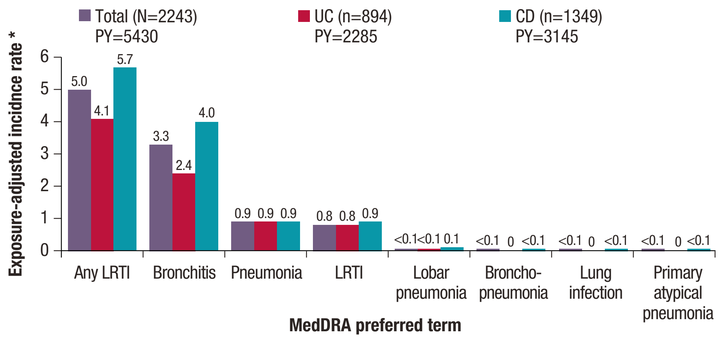
Figure 2. Exposure-Adjusted Incidence Rates of LRTIs in the Pooled GEMINI 1 and 2 Studies



*Exposure-adjusted incidence rate per 100 PY ([number of patients experiencing an AE of interest/total patient exposure time in years] × 100)

AE, adverse event; LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years

Figure 3. Exposure-Adjusted Incidence Rates of LRTIs in the OLE



*Exposure-adjusted incidence rate per 100 PY ([number of patients experiencing an AE of interest/total patient exposure time in years] × 100)

AE, adverse event; CD, Crohn's disease; LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; PY, patient-years; UC, ulcerative colitis

- The rates of serious LRTIs and serious URTIs were low in the pooled GEMINI 1 and 2 analysis and the GEMINI OLE (Table 2)
  - Two LRTIs (vedolizumab group during GEMINI 2) and two URTIs (one in GEMINI OLE and one in GEMINI 2) resulted in discontinuation; 3 out of 4 were considered non-serious
- There were no deaths from upper or lower RTIs in patients treated with vedolizumab, compared with one death in the placebo group

Table 2. RTIs in GEMINI 1, 2 and OLE

	GEMINI 1 and GEMINI 2 pooled				GEMINI OLE	
	Vedolizumab (n=1434) Total PY=1058		Placebo (n=297) Total PY=171		Vedolizumab (n=2243) Total PY=5430	
	All*, n (IR)†	Serious, n (IR)†	All*, n (IR)†	Serious, n (IR)†	All*, n (IR)†	Serious, n (IR)†
Any LRTI	79 (7.7)	5 (0.5)	14 (8.5)	1 (0.6)	248 (5.0)	20 (0.4)
Any URTI	339 (38.7)	2 (0.2)	50 (33.0)	0	857 (23.5)	6 (0.1)
AE leading to discontinuation						
LRTI	2 (0.2)	1 (<0.1)	0	0	0	0
URTI	1 (<0.1)	0	0	0	1 (<0.1)	0
Deaths						
LRTI	0	0	1 (0.6)	1 (0.6)‡	0	0
URTI	0	0	0	0	0	0
LRTIs						
Bronchitis§	57 (5.5)	1 (<0.1)	10 (6.0)	0	170 (3.3)	0
Pneumonia	11 (1.0)	2 (0.2)	2 (1.2)	0	49 (0.9)	18 (0.3)
LRTI	10 (1.0)	1 (<0.1)	1 (0.6)	0	45 (0.8)	0
Lobar pneumonia	0	0	0	0	5 (<0.1)	2 (<0.1)
Bronchopneumonia	1 (<0.1)	0	1 (0.6)	1 (0.6)	1 (<0.1)	0
Lung infection	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	0
Primary atypical pneumonia	1 (<0.1)	0	0	0	1 (<0.1)	0
URTIs						
Nasopharyngitis§	180 (18.6)	0	21 (12.8)	0	485 (10.9)	1 (<0.1)
URTI§	106 (10.5)	0	19 (11.6)	0	298 (6.1)	1 (<0.1)
Sinusitis§	44 (4.3)	1 (<0.1)	3 (1.8)	0	194 (3.8)	2 (<0.1)
Pharyngitis§	24 (2.3)	0	1 (0.6)	0	65 (1.2)	0
Rhinitis	13 (1.2)	0	4 (2.4)	0	34 (0.6)	0
Tonsillitis	5 (0.5)	1 (<0.1)	0	0	25 (0.5)	0
Laryngitis	3 (0.3)	0	2 (1.2)	0	19 (0.4)	1 (<0.1)
Tracheitis	3 (0.3)	0	1 (0.6)	0	2 (<0.1)	0
Acute sinusitis	2 (0.2)	1 (<0.1)	1 (0.6)	0	8 (0.2)	0
Acute tonsillitis	2 (0.2)	0	1 (0.6)	0	16 (0.3)	0
Chronic sinusitis	2 (0.2)	0	0	0	7 (0.1)	0
Tracheobronchitis	1 (<0.1)	0	0	0	1 (<0.1)	0
Rhinolaryngitis	0	0	1 (0.6)	0	0	0
Sinobronchitis	0	0	0	0	2 (<0.1)	0
Peritonsillar abscess	0	0	0	0	1 (<0.1)	1 (<0.1)
Pharyngotonsillitis	0	0	0	0	1 (<0.1)	0

*Includes serious and non-serious AEs

†Exposure-adjusted incidence rate per 100 PY ([number of patients experiencing an AE of interest/total patient exposure time in years] × 100)

‡Patient on placebo died due to bronchopneumonia, which was a serious AE

§AE included in the vedolizumab summary of product characteristics[5]

AE, adverse event; IR, incidence rate; LRTI, lower respiratory tract infection; OLE, open-label extension; PY, patient-years; URTI, upper respiratory tract infection

Predictors of RTIs

- In the pooled GEMINI 1 and 2 studies, significant risk factors for LRTIs were female sex, prior anti-TNFα use and a history of being a smoker (current and former smoker; Figure 4)
  - The proportion of patients who were current smokers was higher in females (19.7%) than males (14.8%) in the pooled GEMINI 1 and 2 population
  - A higher proportion of patients with CD were smokers than those with UC (current smokers: female 29.2% and male 22.3% in the GEMINI 2 study; female 4.2% and male 7.5% in the GEMINI 1 study)
  - Predictors of an LRTI were:

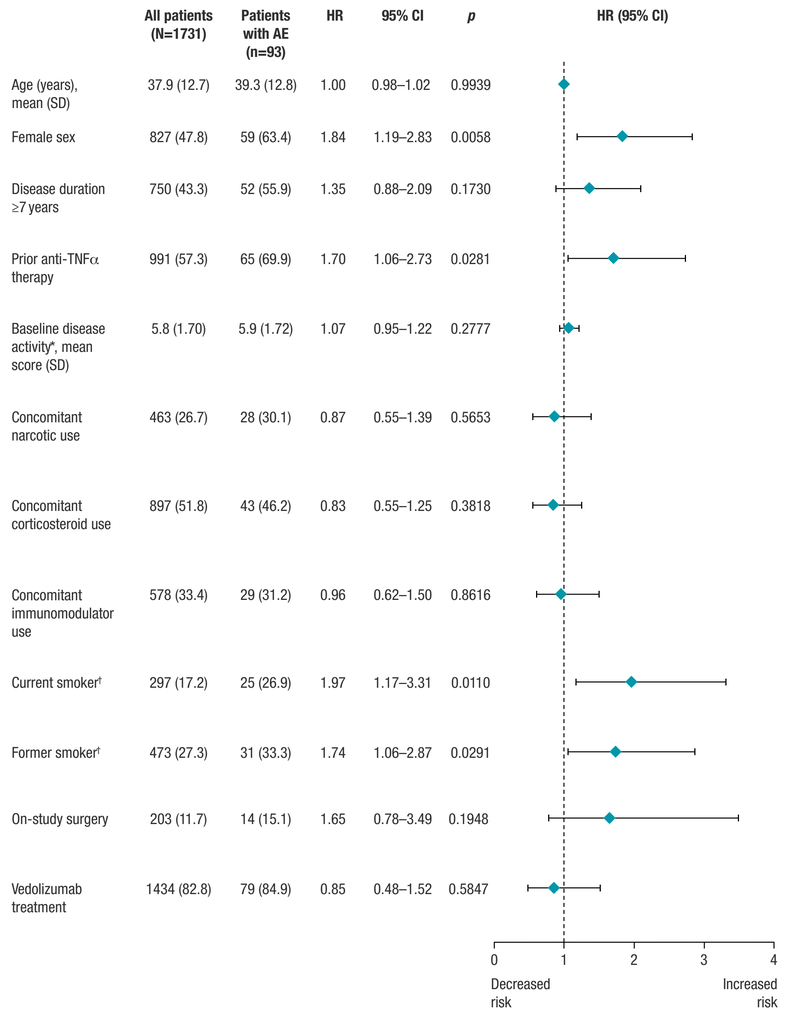
    UC population
    - Female sex (HR: 2.11; 95% CI: 1.07–4.14; p=0.0303)
    - Prior anti-TNFα use (HR: 2.20; 95% CI: 1.10–4.41; p=0.0265)

    CD population
    - Current smoker (HR: 2.37; 95% CI: 1.26–4.45; p=0.0076)
- In the pooled GEMINI 1 and 2 studies, significant risk factors for URTIs were:
  - Current smoker (HR: 1.35; 95% CI: 1.04–1.75; p=0.0225)
  - Concomitant narcotic use (HR: 1.30; 95% CI: 1.04–1.64; p=0.0215)
  - Prior anti-TNFα use (HR: 1.50; 95% CI: 1.20–1.88; p=0.0004)

  UC population
  - Younger age (HR: 0.99; 95% CI: 0.97–1.00; p=0.0177
  - Prior anti-TNFα use (HR: 1.75; 95% CI: 1.28–2.39; p=0.0005)

  CD population
  - Current smoker (HR: 1.60; 95% CI: 1.16–2.19; p=0.0039)
  - Concomitant narcotic use (HR: 1.36; 95% CI: 1.01–1.84; p=0.0451)

Figure 4. Predictors of LRTIs in Pooled GEMINI 1 and 2 Data



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†HR relative to non-smokers

CD, Crohn's disease; HBI, Harvey–Bradshaw Index; LRTI, lower respiratory tract infection; TNFα, tumour necrosis factor-alpha; UC, ulcerative colitis

Conclusions

- In this post hoc analysis, vedolizumab treatment of inflammatory bowel disease was not associated with an increased incidence of LRTIs, including pneumonia, compared with placebo
  - Most LRTIs and URTIs were not serious and did not result in treatment discontinuation
- Patients receiving vedolizumab who were female, had previously used anti-TNFα therapies or were current/former smokers were found to have an increased risk of developing LRTIs
  - The GEMINI trials were not statistically powered to detect these differences
  - Anti-TNFα use[2–4,12,13] and smoking[14] have both been previously shown to increase the risk of pneumonia
- Continuing pharmacovigilance will augment these data and current observational studies will further characterise these findings

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