

IN IT FOR THE LONG HAUL: MANAGING THE COMPLEXITY OF CROHN'S DISEASE

Summary of presentations from the Takeda-Sponsored Symposium held on at the 11th Congress of the European Crohn's and Colitis Organisation (ECCO) in Amsterdam, Netherlands, on 18th March 2016

Chairperson

Michael A. Kamm¹

Speakers

Michael A. Kamm,¹ Remo Panaccione,² Stefan Schreiber³

1. St Vincent's Hospital, Melbourne, Australia

2. Inflammatory Bowel Disease Group, University of Calgary, Calgary, Canada

3. Department of General Internal Medicine, Christian-Albrechts-Universität zu Kiel, University Hospital Schleswig-Holstein, Kiel, Germany

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MEETING SUMMARY

The challenges of, and opportunities for optimal long-term management of Crohn's disease (CD) and real-world experience of managing CD and its application in clinical practice were discussed at this symposium. CD is a complex disease, which requires effective treatment options to improve the quality of life for patients, both in terms of intestinal and extraintestinal manifestations (EIMs). Increased gut permeability of luminal antigens may play a primary role in the pathogenesis of CD, leading to dysregulation of the host's immune response, and resulting in increased levels of tumour necrosis factor (TNF)- α and interferon (IFN)- γ in the inflamed mucosa of patients. Appropriate management goals need to be established by the physician and patient together. Anti-TNF therapy is not suitable for all patients, and a significant proportion of patients will be primary non-responders. Safety must also be considered as part of a patient-tailored assessment. Vedolizumab is a gut-selective antibody to $\alpha 4\beta 7$ integrin for the treatment of ulcerative colitis (UC) and CD. An integrated Phase II and III safety analysis showed that vedolizumab exposure was not associated with increased risk of any infection or serious infection, or any cases of progressive multifocal leukoencephalopathy (PML), a rare and usually fatal viral disease characterised by progressive damage of the white matter of the brain at multiple locations. Data from the GEMINI trials with vedolizumab

showed it to be effective versus placebo, in terms of eliciting both initial and sustained responses, and inducing remission in CD. The real-world studies with vedolizumab in >800 CD patients, most of whom failed ≥ 1 anti-TNF therapy, confirmed the efficacy and safety reported in clinical trials. Up to 30% of CD patients are receiving vedolizumab as a first biologic in the real-world setting.

The Complexity of Crohn's Disease: Implications for Biologic Therapy

Professor Remo Panaccione

CROHN'S DISEASE: COMPLEX AETIOLOGY AND PATHOGENESIS

The aetiology of CD is unknown; there are many proposed pathogenic mechanisms, including genetic predisposition and environmental factors that lead to an imbalance of the host's immune system.¹ As there is no one cause, it is likely that CD is an outcome of interactions between these factors.

Under normal circumstances, the gut epithelium forms a selective barrier, favouring movement of nutrients and regulating movement of ions and water, while limiting contact with luminal dietary antigens and microbes. While the cause of CD is unknown, increased permeability to luminal antigens may play a primary role,² leading to dysregulation of the host's immune response involving several molecules, including cytokines.³ In CD, the major cytokines arise from T helper (Th) 1 and Th17 CD4⁺ T cell differentiation.^{4,5} As a result, levels of Th1 and Th17-related proinflammatory cytokines, including interleukins, TNF- α , and IFN- γ , are increased in the inflamed mucosa of CD patients. IFN- γ recruits leukocytes to the site, and adhesion molecules play an important role in assisting leukocyte migration through endothelial cells.^{4,5} The interaction between mucosal addressin cell adhesion molecule-1 on endothelial cells in the gut and $\alpha 4\beta 7$ integrin on memory T lymphocytes results in the accumulation of excess infiltrating lymphocytes in the gastrointestinal tissue.⁶ This mechanism has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD. It is also important to consider body systems outside of the gastrointestinal tract, as these are also affected by CD.

Extraintestinal symptoms in CD comprise extraintestinal complications and EIMs.⁷ Extraintestinal complications are caused mainly by CD itself and include malabsorption, osteoporosis,

peripheral neuropathies, kidney stones, gallstones, and inflammatory bowel disease (IBD) drug-related side effects.⁷ EIMs most frequently affect the joints (e.g. sacroiliitis, ankylosing spondylitis), skin (e.g. oral aphthous ulcers, Sweet's syndrome, erythema nodosum, pyoderma gangrenosum, peristomal pyoderma gangrenosum), eyes (episcleritis, uveitis), and the hepatobiliary tract (primary sclerosing cholangitis). EIMs less frequently affect the lungs, heart, pancreas, and vascular system.⁷ Treatment options for EIMs are necessary to improve the quality of life of CD patients.

Management of Crohn's Disease

Physicians tend to view management of CD from a long-term perspective. Typical management goals are:

- Avoid surgery (which may be used as a last resort)
- Induce rapid remission with acceptable side effects
- Change the natural history of the disease (avoiding complications)
- Avoid steroid toxicity
- Induce mucosal healing⁸

However, patients view management of their CD from a short-term perspective. Patient priorities are:

- Minimise side effects of the medication
- Minimise symptoms
- Have the opportunity to discuss anxieties with the physician
- Have the opportunity to discuss related issues (fatigue, cosmetic changes, fertility, sexuality, uncertainty)⁸

When considering the available therapies, safety profiles should also be a key consideration. In addition, appropriate management goals need to be established by the physician and patient together.

While anti-TNF agents (e.g. infliximab and adalimumab) have been shown to be effective in controlling inflammation, improving symptoms, inducing mucosal healing, and deep remission, anti-TNF therapy is not suitable for all CD patients.⁸ Safety must be considered as part

of a patient-tailored assessment. Furthermore, the main limitation of anti-TNF therapy is that a significant proportion of patients will be primary non-responders.

Safety of Anti-Tumour Necrosis Factor and Anti- α 4 β 7 Integrin Therapy for the Treatment of Crohn's Disease

In a prospective study of 6,273 CD patients enrolled in the observational Crohn's Therapy,

Resource, Evaluation, and Assessment Tool (TREAT) registry and followed for 5 years, anti-TNF therapy with infliximab was an independent predictor of serious infection (hazard ratio [HR]: 1.43, 95% confidence interval [CI]: 1.11-1.84, $p=0.006$).⁹ Other predictors of serious infection were moderate-to-severe disease activity (HR: 2.24, 95% CI: 1.57-3.19, $p<0.001$), narcotic analgesic treatment (HR: 1.98, 95% CI: 1.44-2.73, $p<0.001$), and prednisone therapy (HR: 1.57, 95% CI: 1.17-2.10, $p=0.002$).⁹

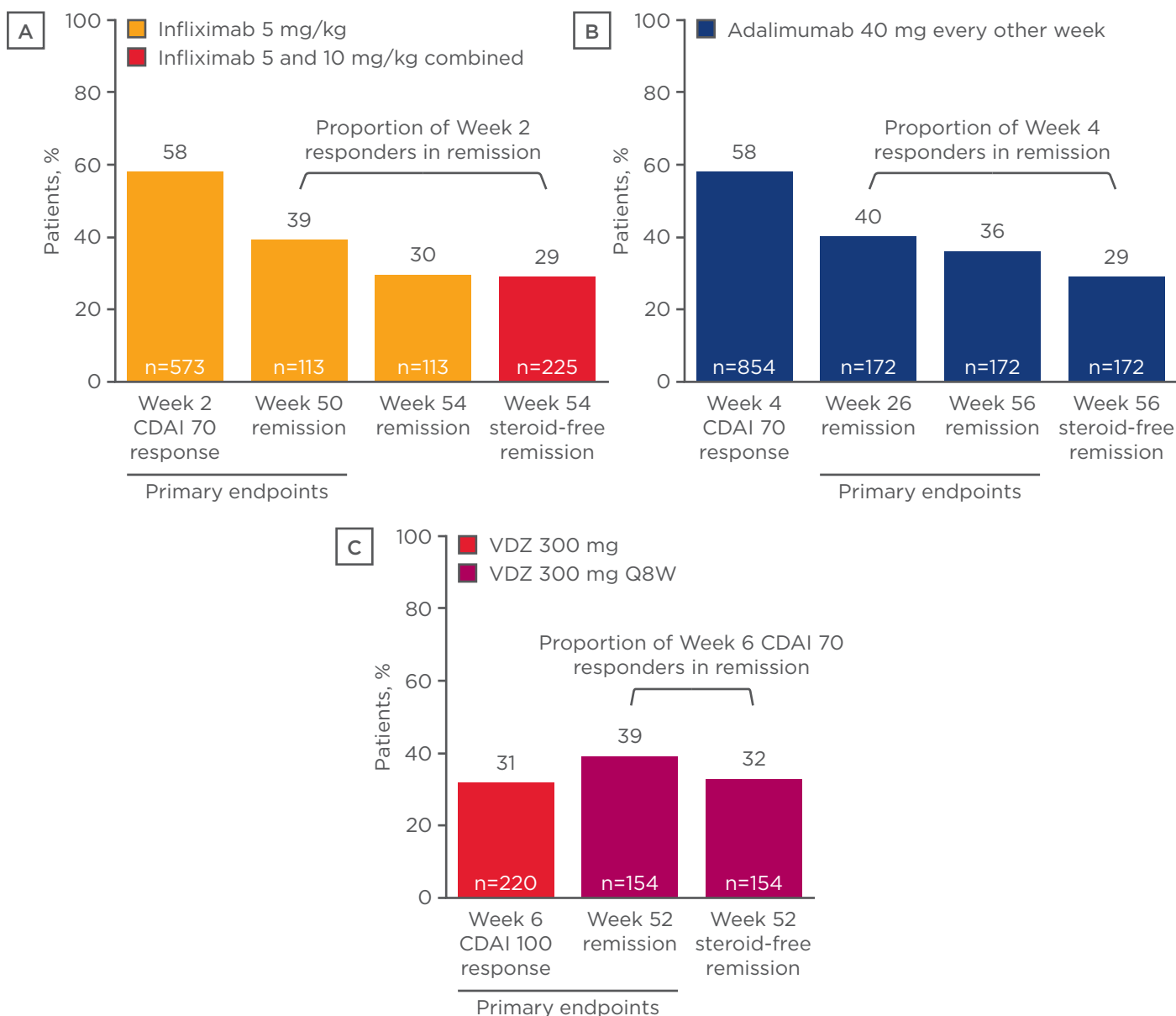
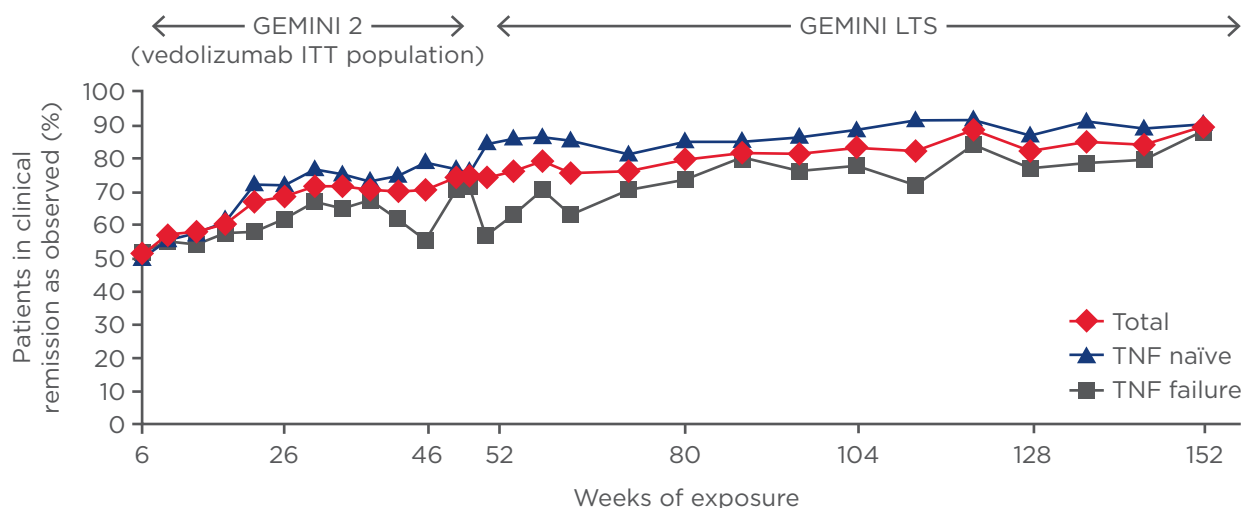


Figure 1: Efficacy of A) infliximab,¹⁷ B) adalimumab,¹⁹ and C) vedolizumab²² in the maintenance of response and remission of moderate-to-severe Crohn's disease.

A) Results from the ACCENT I trial, which included anti-TNF naïve patients; B) results of the GEMINI 2 Phase III study, which included anti-TNF naïve and experienced patients; C) CHARM Phase III study, which included anti-TNF naïve and experienced patients.

CDAI 70 (or 100) response, response defined as the proportion of patients with a reduction of ≥ 70 (or ≥ 100) points in the score on the Crohn's Disease Activity Index.

TNF: tumour necrosis factor; VDZ: vedolizumab; Q8W: every 8 weeks; CDAI: Crohn's Disease Activity Index.



All patients, N	143	141	143	145	134	120	104	70
TNF naïve patients, n	80	76	78	80	74	66	54	31
TNF failure patients, n	56	57	57	57	52	47	44	34

Figure 2: An interim analysis of the rates of clinical remission in the GEMINI long-term safety study (observed cases).²⁴

TNF: tumour necrosis factor; LTS: long-term safety; ITT: intention to treat.

In a prospective cohort study including 3,079 IBD patients, those aged >65 years (n=95) receiving infliximab and adalimumab followed for 10 years were shown to be at high risk of serious infections and death.¹⁰ Incidences of serious infections in older patients were 11% versus 2.6% in patients aged ≤65 years and who did not receive these treatments (n=190), and deaths occurred in 10% versus 1% of patients, respectively.¹⁰

Contraindications for treating with anti-TNF therapy include moderate or severe heart failure (New York Heart Association Class III/IV), tuberculosis, or other severe infections such as sepsis, and opportunistic infections.^{11,12}

An integrated Phase II and III safety analysis of vedolizumab including >2,800 CD patients with a follow-up to 5 years, showed that vedolizumab exposure was not associated with increased risk of any infection or serious infection.¹³ No cases of PML were observed in the integrated Phase II and III safety analysis.¹³ Overall, vedolizumab was well-tolerated by both anti-TNF-naïve and anti-TNF-failure patients.¹³ Another study in healthy volunteers aged 18–45 years showed no significant changes in cerebrospinal fluid T lymphocyte populations 5 weeks after administration of intravenous (IV) vedolizumab 450 mg.¹⁴ However, as PML cannot be ruled out in those treated with vedolizumab, patients should be monitored

for any new or worsening neurological signs or symptoms.¹⁵ Vedolizumab treatment is contraindicated in patients with tuberculosis, sepsis, cytomegalovirus, listeriosis, and PML.¹⁵

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.¹⁵ There are only limited data from the use of vedolizumab in pregnant women.¹⁶ An observational pregnancy registry, enrolling patients with UC or CD on vedolizumab, is currently in development to observe and evaluate the long-term safety of vedolizumab in pregnancy. Vedolizumab is to be used during pregnancy only if the benefits clearly outweigh any potential risk to both the mother and fetus.¹⁵

Efficacy of Anti-TNF and Anti- α 4 β 7 Integrin Therapy for the Treatment of Crohn's Disease

Infliximab

The randomised, controlled ACCENT I trial (ClinicalTrials.gov identifier NCT00207662) assessed the benefit of maintenance infliximab therapy in 573 anti-TNF-naïve CD patients who responded to a single 5 mg/kg IV infusion of infliximab within 2 weeks.¹⁷ The proportion of patients who had a reduction of ≥70 points on the Crohn's Disease Activity Index (CDAI 70 response) at Week 2 was 58% (335/573; Figure 1a). The proportion of Week 2 responders in remission (CDAI <150) at

Week 30 was 21% (23/110) in those who received repeat infusions of placebo (Weeks 2 and 6 and then every 8 weeks thereafter until Week 46), compared with 39% (44/113) in those receiving repeat infusions of infliximab 5 mg/kg at the same time points ($p=0.003$; **Figure 1a**) and 45% (50/112) in those receiving infliximab 5 mg/kg at Weeks 2 and 6 followed by infliximab 10 mg/kg ($p=0.0002$). Thus, patients receiving infliximab maintenance therapy were more likely to sustain clinical remission than patients in the placebo group (odds ratio [OR]: 2.7, 95% CI: 1.6–4.6). Over the 54-week trial period, the median time to loss of response was >54 weeks (interquartile range: 21 to >54) for patients receiving infliximab versus 19 weeks (interquartile range: 10–45) in the placebo group ($p=0.0002$). The proportions of patients who maintained a clinical remission at every visit from Week 14 to Week 54 were 11% (12/110; placebo), 25% (28/113; infliximab 5 mg/kg), and 33% (37/112; infliximab 5 and 10 mg/kg).

Similarly, in a 12-week multicentre, double-blind, placebo-controlled trial of infliximab IV 5, 10, or 20 mg/kg in 108 patients with moderate-to-severe CD that was resistant to treatment, 33% of the infliximab-treated group went into remission (CDAI <150) at 4 weeks versus 4% in the placebo group ($p=0.005$).¹⁸

Adalimumab

In the randomised, double-blind, CHARM Phase III study (NCT00077779), among moderate-to-severe CD patients who responded to adalimumab (80 mg Week 0 followed by 40 mg Week 2), both adalimumab 40 mg every other week (36%) and weekly (41%) were significantly more effective than placebo (12%) in maintaining remission (CDAI <150) through 56 weeks (**Figure 1b**; $p<0.001$ for pairwise comparison between each adalimumab treatment group and placebo).¹⁹ There were no significant differences in efficacy between adalimumab every other week and weekly.

Two Phase III, randomised, double-blind, induction studies showed that adalimumab 160 mg at Week 0 and 80 mg at Week 2 were more effective than placebo in inducing Week 4 remission (CDAI <150; primary endpoint) in patients with moderate-to-severe CD who were either naïve to anti-TNF therapy (36% [27/76] versus 12% [9/74], respectively, $p=0.001$; CLASSIC 1 study)²⁰ or anti-TNF experienced (21% [34/159] versus 7% [12/166], respectively, $p<0.001$; GAIN study).²¹

Vedolizumab

The efficacy of vedolizumab in CD was evaluated in an integrated study (GEMINI 2; NCT00783692) with separate induction (N=1,115) and maintenance trials (N=461).²² The trial recruited patients with complex CD of long disease duration (8–9 years). Approximately 50% of patients had previously received anti-TNF therapy.

In the induction trial, CD patients receiving vedolizumab 300 mg IV were more likely than patients in the placebo group to have a remission (14.5% versus 6.8%, respectively, $p=0.02$) but not a CDAI-100 response (31.4% versus 25.7%, $p=0.23$) at Week 6 (**Figure 1c**). In the maintenance trial, 461 patients who responded to vedolizumab induction therapy and who continued to receive vedolizumab 300 mg every 8 or 4 weeks (Q8W and Q4W; rather than switching to placebo) were more likely to be in remission at Week 52 (39.0% and 36.4% versus 21.6% placebo; $p<0.001$ and $p=0.004$ for the two vedolizumab groups, respectively, versus placebo) (**Figure 1c**).

An exploratory analysis evaluated the efficacy of vedolizumab in the subpopulation of patients with fistulising CD from GEMINI 2.²³ A greater proportion of CD patients with draining fistulae at Week 0 who continued vedolizumab treatment after induction achieved fistula closure at Week 14 compared with those who were re-randomised to placebo (28% versus 11%, respectively), and this effect was maintained through to Week 52. The reported probabilities of fistula closure with vedolizumab were 29% at 6 months and 33% at 12 months.²³ The ENTERPRISE study (NCT02630966) is evaluating the safety and efficacy of vedolizumab for the treatment of fistulising CD.

In the interim, efficacy analyses from the ongoing GEMINI long-term safety study, in which patients received an additional 100-week treatment with open-label vedolizumab Q4W maintenance dosing, clinical remission was observed up to 152 weeks in both patients with prior anti-TNF failure and who were anti-TNF-naïve (**Figure 2**).²⁴ Another retrospective analysis of the GEMINI long-term safety study population that had received vedolizumab for >1 year ($n=23$ CD patients, $n=34$ UC patients) reported that, at the last colonoscopy, 70% of UC patients maintained mucosal healing, and 44% and 38% of CD patients had complete or partial healing, respectively. Results from 32 (CD patients) and 50 (UC patients) colonoscopies

Gut-Selective Biologic Therapy: Translating Clinical Trial Data Into Real-World Clinical Practice

Professor Stefan Schreiber

performed throughout the study and after a median of 2.7 years indicated complete healing (CD patients) and Mayo score 0 (UC patients) in 54% and 44% of colonoscopies, respectively.²⁵

In a placebo-controlled, Phase III, double-blind trial, vedolizumab 300 mg IV was not more effective than placebo in inducing clinical remission at Week 6 among the largest cohort of patients (N=315) with moderate-to-severe CD who previously failed TNF therapy (15.2% versus 12.1%, respectively, $p=0.433$).²⁶ However, a higher proportion of patients receiving vedolizumab had a CDAI-100 response at Week 6 (39.2% versus 22.3%; nominal $p=0.001$; relative risk [RR]: 1.8; 95% CI: 1.2–2.5) and were in remission at Week 10 (26.6% versus 12.1%, respectively; nominal $p=0.001$; RR: 2.2; 95% CI: 1.3–3.6). Although the TNF antagonist-naïve subgroup was relatively small (n=101), a higher proportion of patients receiving vedolizumab than placebo had clinical remission at Week 6 (31.4% versus 12.0%, $p=0.012$; RR: 2.6, 95% CI: 1.1–6.2).²⁶

For most EIMs, the mainstay of therapy is treatment of the underlying active IBD.²⁷ A *post hoc* analysis of GEMINI 2 did not show a statistically significant benefit of vedolizumab versus placebo for the treatment of EIMs in the subpopulation of patients who had EIMs at baseline,²⁸ although there was a trend toward benefit. Kaplan–Meier estimates for resolution of: any EIMs with vedolizumab were 32% at Week 52 versus 23% with placebo, respectively (HR: 1.4; 95% CI: 0.7–2.79); EIMs excluding anal disease-related complications were 43% versus 23% (HR: 1.87, 95% CI: 0.96–3.64); anal disease-related complications were 22% versus 25% (HR: 0.8, 95% CI: 0.18–3.49); and arthritis/arthralgia were 42% versus 26% (HR: 1.84, 95% CI: 0.91–3.71), respectively.

Conclusions

CD is a complex disease with EIMs (e.g. spondyloarthritis, pyoderma, uveitis) and perianal disease, which need to be considered and managed. The patient's fears and concerns need to be respected, and it is important to balance long-term benefit with long-term risk. The benefit-risk profile supports vedolizumab use as a first-line biologic in CD, which is efficacious in anti-TNF-naïve patients, with a durable maintenance effect comparable to that of anti-TNF therapies.

Clinical trial data have shown vedolizumab to be effective, both in terms of eliciting initial and sustained responses, and in inducing remission in UC and CD, as compared with placebo, and vedolizumab was well tolerated across all ages of CD patients.^{22,26,29,30} However, the strict inclusion criteria and other constraints used in randomised, controlled trials may limit generalisation of data from the GEMINI trials to the real world. The experience with vedolizumab in real-world studies is described below. The studies included >40 CD patients and reported clinical outcomes including response, remission, or change in CDAI or Harvey–Bradshaw index (HBI). All studies were predominantly in refractory populations (Table 1).

Shelton et al.: Massachusetts General Hospital and Boston Brigham and Women's Hospital

The efficacy of vedolizumab in IBD was evaluated at Week 14 in a multicentre cohort of patients with HBI >4 (CD) or Simple Clinical Colitis Activity Index (SCCAI) >2 (UC) at Boston Massachusetts General Hospital (MGH; prospective study) and Brigham and Women's Hospital (BWH; retrospective study).³¹ Vedolizumab 300 mg was administered at Weeks 0, 2, 6, and 8.

The primary endpoint was response or remission at Week 14. For CD, response was defined as a reduction of HBI ≥ 3 or reduction of SCCAI ≥ 3 (MGH) or 'physician defined' response (at BWH). Remission was defined as HBI ≤ 4 or SCCAI ≤ 2 (MGH) or 'physician defined' remission (BWH).

The study included 107 CD patients (Table 1) (MGH: N=46; BWH: N=61), of whom 48% were men. Patients with a pouch or stoma were excluded. Most CD patients had received previous treatment with ≥ 2 anti-TNF agents (77%), and 39% received corticosteroids at induction. In CD, 49% of patients demonstrated clinical response, similar to what was seen in clinical trials, 24% achieved clinical remission, and 19% achieved steroid-free remission at Week 14. In a multivariate analysis, prednisolone at induction (OR: 0.34, 95% CI: 0.10–1.18; $p=0.08$) and C-reactive protein >8.0 mg/L at induction (OR: 0.33, 95% CI: 0.11–0.96, $p=0.04$) were found to be predictors of response/remission (composite endpoint) at Week 14 in IBD.

Table 1: Summary of the data for vedolizumab in real-world studies.

Study	Number of patients receiving vedolizumab			Baseline characteristics of CD patients (unless stated)				Efficacy in CD at Week 14 (or when stated)	
	IBD	UC	CD	Age, years	Disease duration, years	≥2 prior anti-TNF agents, %	Concomitant IMM at first dose, %	Response, (C) %	Remission, (D) %
Shelton et al. ³¹ (Boston MGH and BWH)	172 (A)	59	107	39.7 mean	16.4 mean	77	32	49 (E)	24 (E)
Amiot et al. ³² (French early access programme)	294	121	173	37.3 mean	712.1 mean	99 (≥1 TNF agent)	15 IMM only	64	36
Baumgart et al. ³³ (German registry)	212	115	97	36 median	9 median	75	80 IMM only	62	24
Eriksson et al. ³⁴ (Swedish IBD registry)	100	33	64	40 median	8 median	66	23	33 (Week 10)	-
Chaparro et al. ³⁵ (Spanish multicentre nationwide study)	71	29	42	43 mean (all IBD)	10.7 mean (all IBD)	93% refractory to biologics	39 (all IBD)	62	14
Chaudrey et al. ³⁶ (Mayo Clinic, Rochester, Minnesota)	63	12	51	NR	NR	96 (≥1 TNF agent)	17	70 (overall; E)	-
Dulai et al. ³⁷ (a US Multicentre Consortium)	141	59	82	39 mean	10 median	74	37	35 (Week 30; F)	31 (Week 30; F)
Lucci et al. ³⁸ (a US referral centre)	62	12	48	38 mean	19 mean	73	NR	48 partial response (≥12 weeks; E, G)	18 (≥12 weeks; E, G)
Christensen et al. ³⁹ (University of Chicago)	130 (69; B)	27	42	NR	11 median	59	NR	58 (H)	39 (H)
Total	1,351	517	783						

A) Six patients IBD-unclassified; B) 130 patients started vedolizumab; 69 reached the 14-week time point at abstract submission; C) response defined as a reduction of HBI ≥ 3 ; D) remission defined as HBI ≤ 4 (MGH) unless otherwise stated; E) physician defined response or remission (Brigham and Women's Hospital [BWH], and Mayo Clinic); F) response defined as >50% reduction in symptoms; remission defined as complete resolution of all symptoms; response remission determined in G) 33 IBD patients on vedolizumab for at least 12 weeks; H) 26 CD patients with active disease at baseline.

MGH: Massachusetts General Hospital; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; TNF: tumour necrosis factor; IMM: immunomodulator; NR: not reported; HBI: Harvey-Bradshaw index.

Vedolizumab was generally well tolerated in IBD patients overall; 18 patients (10.5%) experienced adverse events (AEs). No systemic infections or sepsis occurred.

Amiot et al.: French Early Access Programme

Between June–December 2014, 173 CD patients and 121 UC patients were included in a

French multicentre, nominative, compassionate, vedolizumab early access programme.³² Patients had previously shown an inadequate response to, lost response to, or were intolerant to either conventional therapy or ≥ 1 anti-TNF agent, HBI > 4 (CD) or Mayo clinic score ≥ 6 (UC). Patients received induction therapy with vedolizumab 300 mg IV at Weeks 0, 2, 6, and maintenance Q8W.

The primary endpoint was steroid-free remission at Week 14 with remission defined as HBI \leq 4 (CD) or partial Mayo score $<$ 3, with a combined stool frequency and rectal bleeding subscore \leq 1 (UC).

Regarding the 173 CD patients, 37% were men, and nearly all patients had previously received \geq 1 anti-TNF agents (Table 1) or immunosuppressants. Regarding concomitant therapy, 34% received glucocorticoids only, 15% immunomodulator (IMM) only, and 10% received both glucocorticoids and IMM.

At Week 14, the HBI score in CD patients was significantly ($p < 0.001$) reduced versus baseline; 64% of CD patients had a response (reduction of HBI \geq 3), 51% had a steroid-free response, 36% had clinical remission (HBI \leq 4), and 31% were in steroid-free remission (primary endpoint) (all $p < 0.005$ versus Week 6 except for clinical remission). Vedolizumab had an acceptable safety profile, with 32% of patients reporting AEs. There were no deaths; 24 patients (8%) experienced severe AEs, and 15 (5%) discontinued vedolizumab (within these, there was one case of pulmonary tuberculosis and one rectal adenocarcinoma).

Baumgart et al.: German Registry

Baumgart et al. conducted a nationwide, consecutive, German cohort study (VEDOibd) at 17 private and 7 academic centres including 318 patients (active UC [partial Mayo $>$ 4], N=165; active CD [HBI $>$ 7], N=174) newly receiving vedolizumab 300 mg IV induction at Weeks 0, 2, 6, and maintenance Q8W, and followed for 14 weeks.³³ At baseline, most CD patients were bio-experienced (Table 1), and received steroids (84.5%), IMM only (80%), or both IMM and steroids (62%). By Week 14, 14 patients stopped vedolizumab due to side effects (n=3), failure (n=3), and loss to follow-up (n=8).

At Week 14, the median HBI score in CD patients was reduced versus baseline. Using a non-responder imputation analysis, there were improvements in clinical remission rates (HBI \leq 4) from Week 6 (16%) to Week 14 (primary endpoint; 24%), as well as in steroid-free remission (12% and 20%, respectively); 66% and 61%, respectively, had a clinical response (reduction of HBI \geq 3). Clinical remission at Week 14 was significantly ($p \leq 0.05$) higher in TNF-naïve (60%) than TNF-experienced patients (21.7%). There was a significant steroid-sparing effect, with significantly fewer CD patients

receiving steroids at Week 14 versus Week 6 ($p \leq 0.001$) and versus baseline ($p \leq 0.05$). Regarding the impact of vedolizumab on inflammation markers, there was a significant reduction ($p \leq 0.01$) in calprotectin, but not in C-reactive protein level, at Week 14 versus Week 6. Vedolizumab was well tolerated. The most frequent spontaneously reported AEs were arthralgia, acne, and arthritis, each occurring in nine patients.

Other Vedolizumab Real-World Experience: European Union

In the Swedish IBD registry, clinical response (reduction of HBI \geq 3) was reported for 33% (4/12) of CD patients with recorded clinical disease activity at baseline and after a median follow-up of 10 weeks (range 0–21 weeks).³⁴ After Week 14 in the Spanish multicentre study, 62% responded to treatment and 14.3% were in remission within the 42 CD patients evaluated.³⁵

Other Vedolizumab Real-World Experience: United States

At the Mayo Clinic, physician-defined response rates for CD at induction and overall were 61% and 70%, respectively.³⁶ Most patients with CD had a partial response, defined as 25–50% reduction in symptoms (58% at induction and 49% overall). A summary of efficacy data at the other centres in the USA is presented in Table 1. In studies in the USA, mucosal healing with vedolizumab has been observed in 17–100% of IBD patients, predominantly in refractory populations.^{36,37,40–42} At two centres, endoscopic healing occurred in 30%⁴² and 52%⁴⁰ of patients. In the USA, 16–37% of CD patients receive vedolizumab as their first biologic treatment.^{43–47}

Summary of Vedolizumab Real-World Experience in Patients with Crohn's Disease

The multiple 'real-practice cohorts' included $>$ 800 CD patients, most of whom failed \geq 1 anti-TNF therapy. While cohort sizes are relatively small with a heterogeneous phenotype, the real-world data confirm the efficacy and safety for vedolizumab observed in clinical trials. Real-world data show that up to 30% of patients with CD receive vedolizumab as a first-line biologic. More data on mucosal healing and quality of life are required. Real-world evidence indicates that vedolizumab results in an improvement of disease activity, decrease of steroid usage, and reduction in inflammation markers.

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