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INSIDE

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

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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 $\alpha4\beta7$ 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 α4β7 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 healing[8]

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-α4β7 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]

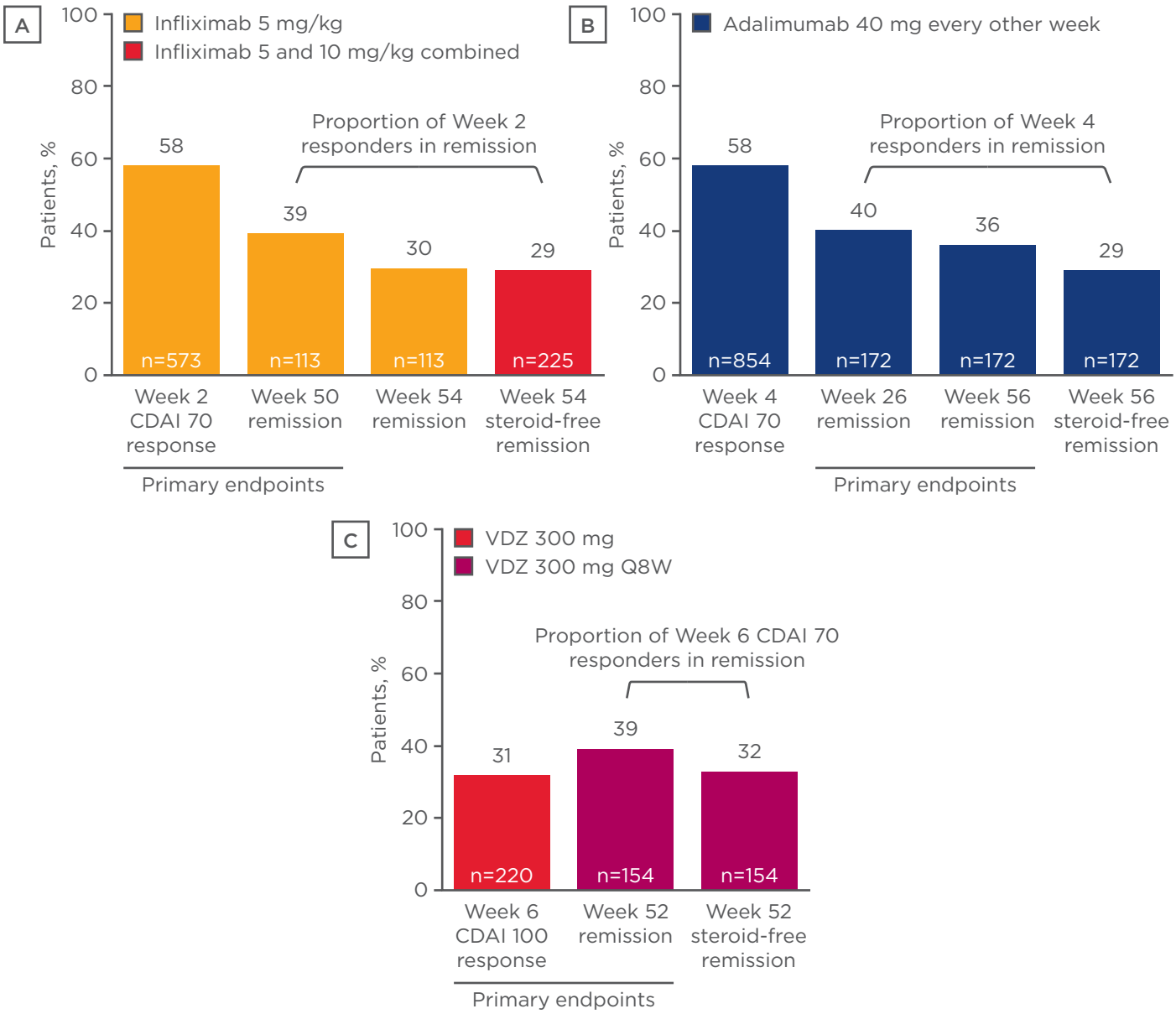
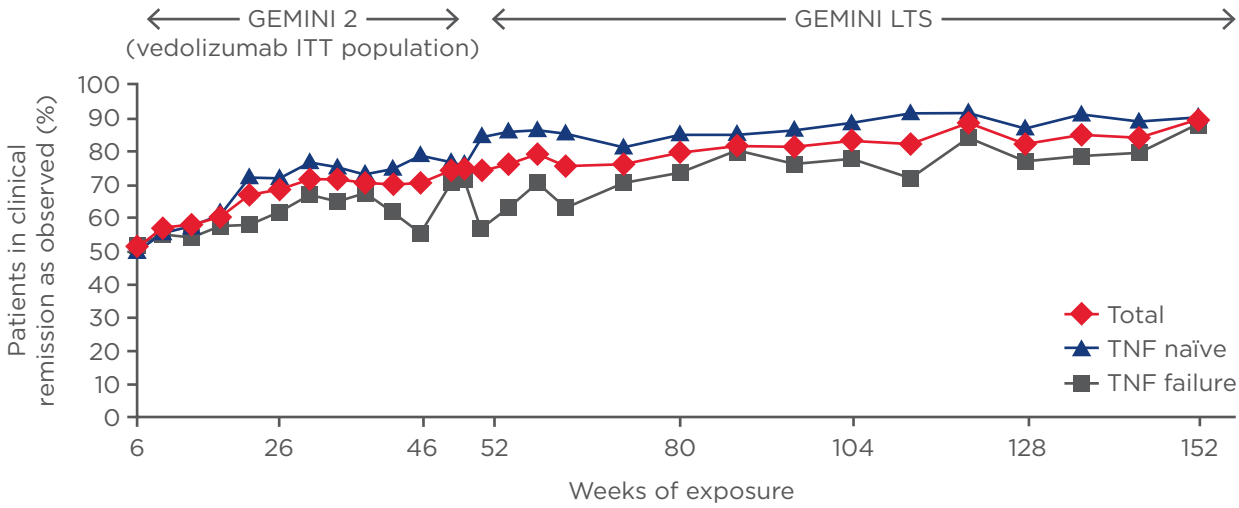


Figure 1: Efficacy of A) infliximab,[17] B) adalimumab,[19] and C) vedolizumab[22] in the maintenance of response and remission of moderate-to-severe Crohn's disease.

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-α4β7 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

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.

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

Professor Stefan Schreiber

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.

	Number of patients receiving vedolizumab			Baseline characteristics of CD patients (unless stated)				Efficacy in CD at Week 14 (or when stated)	
Study	**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 ≤4 (CD) or partial Mayo score <3, with a combined stool frequency and rectal bleeding subscore ≤1 (UC).

Regarding the 173 CD patients, 37% were men, and nearly all patients had previously received ≥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 ≥3), 51% had a steroid-free response, 36% had clinical remission (HBI ≤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 ≤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 ≥3). Clinical remission at Week 14 was significantly (p≤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≤0.001) and versus baseline (p≤0.05). Regarding the impact of vedolizumab on inflammation markers, there was a significant reduction (p≤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 occuring in nine patients.

Other Vedolizumab Real-World Experience: European Union

In the Swedish IBD registry, clinical response (reduction of HBI ≥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 recieve 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 ≥1 anti-TNF therapy. While cohort sizes are relatively small with a heterogenous phenotype, the real-world data confirm the efficacy and safety for vedolizumab observed in clincial 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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MANAGEMENT OF ULCERATIVE COLITIS: PUTTING PATIENTS AT THE CENTRE

Summary of presentations from the Takeda-sponsored symposium at the 11th Congress of the European Crohn's and Colitis Organisation, held in Amsterdam, Netherlands on 18th March 2016

Chairperson

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MEETING SUMMARY

The treatment landscape of ulcerative colitis (UC) is changing, with new treatment options becoming available and insights into disease management demonstrating the importance of a patient-centric approach. Induction and maintenance of long-term remission are important treatment goals. However, some of the current treatment options often have limited efficacy, which may be coupled with an unfavourable safety profile, such as an increased risk of infection. A multiphase approach to disease management, which includes induction and maintenance of remission through close monitoring, is a viable clinical strategy. Selecting an appropriate first-line therapy is a crucial part of this strategy, as options are sometimes limited for patients who have failed anti-tumour necrosis factor (TNF) therapy. The integrin antagonist, vedolizumab, has demonstrated effective induction and maintenance of clinical remission in both anti-TNF-naïve and anti-TNF-failure patients, with no increase in infection risks. Therefore, vedolizumab should be considered for inducing and maintaining remission as part of a patient-centric disease management programme. The development of simplified monitoring systems that provide an indication of endoscopic activity will also aid patients in taking charge of their disease management. In conclusion, putting our patients at the centre of a proactive model of disease management can help prevent complications in the long-term, and selecting suitable first-line therapies is an important step in this process.

Introduction

Doctor Iris Dotan

Management of UC is changing. Until 2013, mesalazine (5-aminosalicyclic acid) and steroids were the most commonly used treatments.[1] However, the advent of new treatments, advances in surgical procedures, and new approaches to disease management including the use of multidisciplinary teams, means that we now have a broader range of options for our patients. This meeting explored methods of implementing these strategies into a framework that will benefit patients and involve them in their disease management.

Partnering with Patients to Optimise Treatment Outcomes in Ulcerative Colitis

Doctor Peter Irving

There have been rapid advances in the management of inflammatory bowel disease (IBD) in the past 15 years. This has been partly driven by the development of new treatments and firmer remission endpoints being defined. However, an unmet need remains for the management of active UC. Many patients have ongoing disease activity, and approximately 50% of UC patients will have an unfavourable disease course.[2] With current medical treatment, 50% of patients relapse within the first year after diagnosis, and after 3–7 years 18% of patients experience a relapse every year.[3] These relapses cause significant disruption in the lives of patients with UC, with a recent survey indicating that ~45% of patients spend more time at home and ~40% cut back on their social life or change their work life to compensate for UC.[4] Considering the impact on the patient is crucial, as physicians often underestimate the effect of UC on individuals' lives and mental wellbeing.[5]

Several options are currently available for the treatment of UC. While steroids are effective induction agents, they are inappropriate for maintenance therapy.[1] This class of drug is associated with side effects such as acne, osteoporosis, and Cushing's syndrome, and as a result steroids are disliked by both patients and physicians.[1] In contrast, thiopurines have been shown to be inefficient as induction agents.[6] A meta-analysis of seven studies indicated that thiopurines were beneficial in maintaining clinical remission with an odds ratio (OR) of 2.56 (95% confidence interval [CI]: 1.51–4.34) showing that treatment favours azathioprine plus mercaptopurine versus placebo or mesalazine.[6] However, this class of drug demonstrated no benefit in induction of remission versus placebo.[6]

Current treatment regimens using therapies such as thiopurines or TNF antagonists have been associated with limited efficacy. The randomised, double-blind, UC SUCCESS trial evaluated the efficacy of 16 weeks of treatment with the TNF antagonist; infliximab; the thiopurine, azathioprine; or a combination of the two drugs. The study included both patients who had failed previous anti-TNF therapy, and anti-TNF-naïve patients. Overall, 40% of patients treated with infliximab and azathioprine achieved steroid-free remission at Week 16, compared with 24% of patients treated with azathioprine (p=0.032) and placebo, and 22% of patients treated with infliximab and placebo (p=0.017).[7] In the randomised, multicentre, double-blind, placebo-controlled, Phase III ULTRA 2 study, anti-TNF-naïve and anti-TNF-failure patients were treated with adalimumab or placebo. The proportion of patients treated with adalimumab who were in clinical remission at Week 8, defined as a Mayo score of ≤2 with no individual subscore of ≥1, was 9.2% in anti-TNF-failure patients and 21.3% in anti-TNF-naïve patients.[8] At Week 52, 10.2% of anti-TNF-failure patients and 22.0% of anti-TNF-naïve patients were in clinical remission.[8] While response rates were low, they were significantly greater than placebo in anti-TNF-failure patients at Week 52, and in naïve patients at both Week 8 and Week 52.[8] The TNF antagonist, golimumab, was investigated as a maintenance therapy in the PURSUIT study versus placebo.[9] The results of this Phase III, double-blind study show that golimumab maintenance therapy at 50 mg and 100 mg doses produced significantly greater rates of durable clinical remission (23.2% and 27.8%, respectively), compared with patients treated with placebo (15.6%, p<0.05).[9] However, the overall rates of response to therapy were still low.[9]

Along with limited efficacy, some of the current therapies have been associated with safety and tolerability issues. The TREAT Registry indicates that patients with Crohn's disease treated with prednisone therapy (hazard ratio [HR]: 1.57; 95% CI: 1.17–2.10, p=0.002) or narcotic analgesic treatment (HR: 1.98; 95% CI: 1.44–2.73, p<0.001) had an increased risk of developing a serious infection.[10]

TNF antagonists have also been shown to double the risk of developing an infection. A meta-analysis of 22 randomised controlled studies found that the relative risk of developing an opportunistic infection with an anti-TNF drug was 2.05 (95% CI: 1.10–3.85) compared with placebo.[11] Safety issues associated with thiopurines include an increased risk of developing skin cancer and lymphoma. A prospective, observational study in 19,486 IBD patients found that treatment with azathioprine increased the risk of developing lymphoma with a yearly incidence rate of 5.41 per 1,000 patient/years of lymphoma in patients >65 years who are on continuing therapy.[12] An increased risk of non-melanoma skin cancer was also associated with thiopurine therapy, with a yearly incidence rate in patients >65 years of 4.04 per 1,000 patient/years in those on therapy and 5.70 per 1,000 patient/years in patients who discontinued therapy.[13]

UC is a progressive disease and it is important to not only treat patients, but to treat beyond the symptoms despite the limited efficacy and unfavourable safety profiles of some therapeutic options. As UC progresses, the risk of developing colorectal cancer increases.[14] Increases in the colonoscopic inflammation score or histological inflammation score are significantly associated with an increased risk of colorectal cancer.[15] Additionally, physicians need to be aware that early treatment outcomes can be predictive of the long-term course of the disease.[16] A multivariate analysis of a cohort of patients with moderate-to-severe, newly-diagnosed UC found that patients with a complete response to treatment at Month 3 had a significantly lower likelihood of hospitalisation (p=0.033) or immunosuppression therapy (p=0.0029) at 5-year follow-up, compared with patients who had partial or no response at Month 3.[16] A cohort of patients in Norway also demonstrated that long-term mucosal healing can significantly reduce the numbers of colectomies and resections in UC patients at 1 year (p=0.02).[17] Therefore, patients who are in remission earlier are more likely to have favourable outcomes in later years.[16,17]

Aiding patients in monitoring their disease themselves can be beneficial in ensuring that therapeutic intervention occurs in a timely fashion. For example, utilising non-invasive disease markers can be a useful strategy for self-monitoring. The biomarker faecal calprotectin has 91% sensitivity and 90% specificity for endoscopic activity. Analysis of faecal calprotectin levels can be carried out by patients at home, allowing them to actively participate in their disease management.[18]

In conclusion, UC is an active disease with a substantial impact on patients' quality of life. While the treatment landscape is changing with more therapies becoming available, issues with the efficacy and safety of current treatments remain. Despite the current unmet needs regarding treatment of UC, it is important to manage active disease in patients to reduce the risk of later complications.

Biologic Therapy Options for Ulcerative Colitis in a Patient-Centric Treatment Paradigm

Professor David T. Rubin

Currently, not all patients achieve the preferred treatment outcomes. This could be due to therapy being initiated too late, the limited efficacy of therapies, therapies not being optimised, an incorrect diagnosis, or the patient simply being satisfied with an improvement in symptoms. It is important to realise that treatment for UC is not 'one size fits all'. In addition, current treatment algorithms require patients to either fail treatment or experience adverse events before switching. This stepwise approach to treatment has been shown to be inadequate and unhelpful for patients. Treatment algorithms for UC are now evolving to reflect this, and shifting towards treat-to-target with less emphasis on systemic treatment and more on targeted therapies.[19-21] When initiating therapy, it is important to analyse the risks and benefits of a therapy, optimise treatment, and to avoid ignoring active inflammation. A five phase management system can be used to help control chronic diseases such as UC: pre-treatment assessment, induction, maintenance, monitoring, and cessation.[22]

PRE-TREATMENT ASSESSMENT

Early aggressive therapy should be considered in patients with UC who display predictors of poor medical response. These predictors can be broadly separated into two categories: quantifiable predictors and symptomatic indicators. Quantifiable predictors of poor medical response include low serum albumin, erythrocyte

sedimentation rate >30 mm/hour, heart rate >90 bpm, and increased C-reactive protein.[23,24] In addition, prolonged flare, active infections, severe endoscopic lesions, and a high percentage of bloody stools can be symptomatic predictors of poor medical response.[23,24]

INDUCTION AND MAINTENANCE

An appropriate treatment should be selected and initiated based on the patients' needs. Several treatment options are available including steroids, TNF-antagonists, cyclosporine, and integrin antagonists. As discussed in the previous presentation, certain treatment options are more appropriate for the induction of remission or for its maintenance. These treatment goals need to be considered alongside a patient's treatment history when initiating a new therapy.

In patients with steroid-refractory UC, treatment options are more limited. The use of cyclosporine or the anti-TNF therapy, infliximab, in patients with severe UC that had been unsuccessfully treated with steroids showed similar efficacy.[25] Data from the CYSIF study demonstrated that the 1-year, colectomy-free survival rates were similar for cyclosporine (71%) and infliximab (70%).[26] This similarity was maintained for the 5-year, colectomy-free survival rates of 62% versus 65%, respectively.[26]

An alternative treatment for patients with moderate-to-severe UC is anti-α4 integrins. Vedolizumab is a monoclonal antibody that targets the α4β7 integrin in the gut-tropic T cell and prevents migration of the lymphocyte into the gut mucosa.[27] In the Phase III, randomised, double-blind, placebo-controlled GEMINI I study, patients received either vedolizumab 300 mg or placebo intravenously at Weeks 0 and 2 in cohort 1, and a second cohort (cohort 2) received open-label vedolizumab at Weeks 0 and 2, with disease evaluation at Week 6.[28] Patients in either cohort who responded to vedolizumab were randomised to receive either vedolizumab or placebo every 8 or 4 weeks for up to 52 weeks. A response was defined as a reduction in Mayo Clinic score of ≥3 and a reduction from baseline of ≥30%, in addition to an accompanying reduction in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of 0 or 1.

Both anti-TNF-naïve and anti-TNF-failure patients were enrolled in the study. Vedolizumab met the primary induction endpoint of the study as it demonstrated significant improvement in clinical response at Week 6 in both anti-TNF-naïve and anti-TNF-failure patients compared with placebo (47.1% versus 25.5%, p<0.001; Figure 1).[28] Secondary induction endpoints of clinical remission (16.9% versus 5.4%, p=0.01) and mucosal healing (40.9% versus 24.8%, p=0.001) were also met (Figure 1).[28] Maintenance data from the same study indicated that at Week 52, 4-weekly vedolizumab significantly improved Mayo Clinic scores and glucocorticoid use in patients, compared with placebo (p<0.001).[28] Data from the long-term safety study, where patients were treated with 4-weekly vedolizumab, indicated that at Week 52, 65.8% of patients who completed the GEMINI I study were in clinical remission.[29] This proportion increased to 77.1% at Week 80, and at Week 104 72.7% of patients remained in clinical remission.[29] The proportion of patients who had failed previous anti-TNF therapy in remission (65.3%) was slightly lower compared with anti-TNF-naïve patients (76.7%).[29]

A meta-analysis of seven studies of several treatments including TNF antagonists and vedolizumab indicated that therapy favours vedolizumab over placebo as both first-line induction therapy (OR: 4.5) and first-line maintenance therapy (OR: 3.6; Figure 2).[30] However, the differences in study designs and patient characteristics means it is not possible to make a direct comparison between post-approval studies, limiting the usefulness of the meta-analysis.

Following licensing in Europe and the USA in 2014, increasing amounts of data on the post-approval experience with vedolizumab are now available. There is a variation in response rates, but overall the data from the real-world studies resemble the outcomes of the clinical trial (Table 1). Response rates varied from 15% at Week 12 in a US consortium to 57% at Week 14 in a multicentre study in France.[31,32]

When selecting a first-line therapy, any safety concerns associated with treatment should also be considered. An integrated safety summary of six studies of vedolizumab with up to 5 years of follow-up indicated that this treatment did not result in an increased risk of infection or serious infection versus placebo, with a median exposure range of 1–1,977 days.[33] No reports of progressive multifocal leukoencephalopathy were observed with vedolizumab treatment.[33]

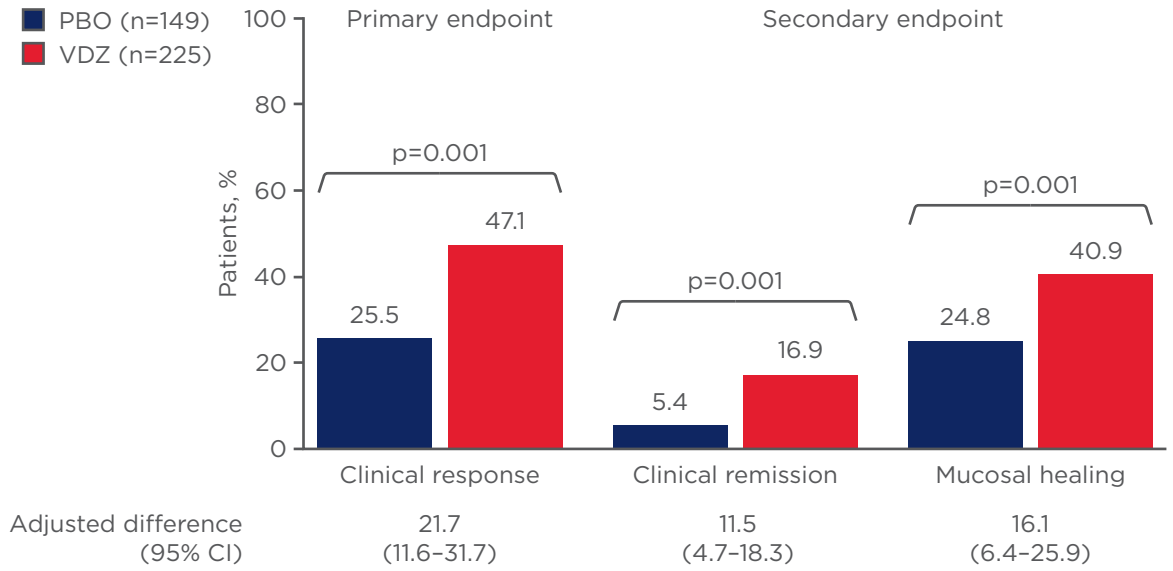

Figure 1: Rates of clinical response, clinical remission, and mucosal healing at Week 6 in the Phase III GEMINI I study of vedolizumab in ulcerative colitis.[28]

PBO: placebo; VDZ: vedolizumab; CI: confidence interval.

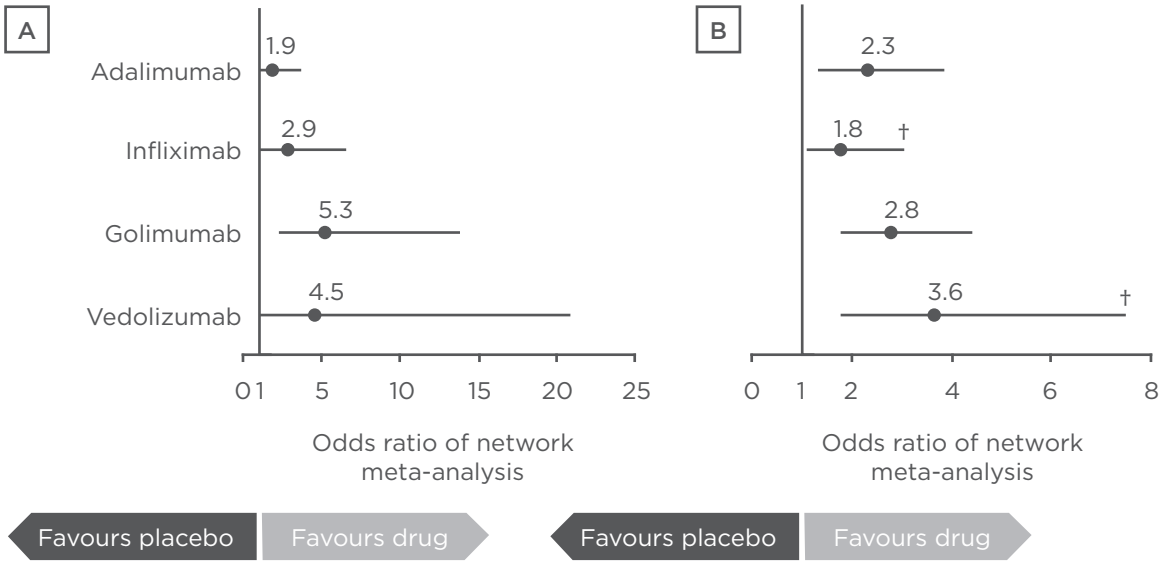

Figure 2: Results of a meta-analysis of seven studies of induction and maintenance therapy in ulcerative colitis: odds ratio of the network meta-analysis.

A) Induction therapy: clinical remission compared with placebo; B) maintenance therapy: clinical remission compared with placebo.

†The study design in the golimumab and vedolizumab trials differed from the adalimumab and infliximab trials; the maintenance therapy phases included only patients who responded to induction therapy.

Optimising therapy is a key component of obtaining and maintaining favourable outcomes for our patients. Optimisation could involve combining treatments, or adjusting the dose or frequency of therapy.[34] Additionally, monitoring of early responses to treatment can be useful in predicting longer term outcomes and aid in swapping or cycling treatments.[35,36] One proposed algorithm is to increase doses of TNF antagonists or reduce dose intervals in patients with a poor response and undetectable or low levels of anti-TNF who do not have anti-drug antibodies. Conversely, patients with a poor response with high anti-TNF levels and who have anti-drug antibodies should be switched to another class of drug.[37]

Table 1: Post-approval experience with vedolizumab.

Study	N	Number of UC patients (%)	Response rate		
			Week 6	Week 14	Week 30
University of Chicago[41]	130 (69)*	39		CD: 58% UC: 50%	CD: 60% UC: 52.9%
Cedars-Sinai Medical Center[42]	66	26	IBD: 49%	IBD: 42%	IBD: 33
Swedish IBD Registry[43]	100	33		At FU (median 10 weeks) CD: 33% UC: 40%	
Boston Experience (MGH & BWH)[30]	172	34		CD: 48.9% UC: 53.5%	
French Multicentre Experience (GETAID)[44]	294	41	CD: 57% UC: 41%	CD: 64% UC: 57%	
Washington University[45]	51	41	CD HBI score: 8.9 (BL 9.3) UC partial Mayo score: 2.9 (BL 5.5)	CD HBI score: 6.9 UC partial Mayo score: 2.6	
Boston University[46]	30	33	CD HBI score: 5.4 UC SCCAI score: 4.4		
US Consortium[31]	141	42		Week 12 CD: 5% UC: 16%	Week 30 CD: 35% UC: 73%

CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; FU: follow-up; HBI: Harvey–Bradshaw Index; SCCAI: Simple Clinical Colitis Activity Index; BL: baseline; MGH: Massachusetts General Hospital; BWH: Brigham and Women's Hospital.
*130 patients started vedolizumab; 69 reached the 14-week time point at abstract submission.

Serial adjustments in therapy in patients with persistent endoscopic activity have been associated with mucosal and histological healing, highlighting the need for consistent control of IBD.[38] A study by Bougen et al.[38] in 60 patients who received any adjustment in medical therapy with at least two consecutive endoscopic assessments, found that 60% of patients with baseline endoscopic activity and 50% of patients with histological disease at baseline achieved mucosal healing. These data indicate that treat-to-target is a feasible clinical strategy for UC.[38]

MONITORING AND REGAINING CONTROL

It is important to understand why patients do not respond to certain therapies to ensure that they are switched to an appropriate alternative. Once a patient reaches target, close monitoring is essential to identify potential subclinical relapse and to identify possible disease progression. Smartphone applications that are able to read the results of faecal calprotectin levels are in development and could aid patients in managing their disease.[39]

CESSATION

Monitoring strategies are not only needed for disease progression but are also useful in planning for potential de-escalation of treatment. However, there are currently few data available on de-escalation in UC.[40] Prior to de-escalation, deep remission of UC must be confirmed and patients should be aware of the risks of reducing their treatment doses or dose intervals, including the potential for relapse or the possibility that there will be a loss of response to their current therapy.[40] In addition to a monitoring strategy, physicians must also have a 'rescue' strategy planned to prevent any disease progression that may result from a change of therapy.[40]

Conclusion

Employing a patient-centric chronic disease management model is key to ensuring that disease targets are not only achieved but also maintained. Treatments should be tailored to the needs of individual patients with well-defined response targets from the outset. In addition, understanding disease prognosis is an important aspect of selecting an appropriate therapy.

The anti-α4 integrins are a novel therapy and offer an alternative option for patients. The integrin antagonist, vedolizumab, is a monoclonal antibody that targets α4β7 integrin in the gut-tropic T cell, preventing migration of lymphocytes to the gut mucosa. Vedolizumab has proven efficacy in both induction and maintenance therapy along with a favourable safety profile, which has been demonstrated in both clinical trials and real-life studies.

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