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INSIDE

CHANGING THE GAME IN ULCERATIVE COLITIS: THE IMPACT OF GUT-SELECTIVE THERAPY

This satellite symposium took place on 17th February 2017 as part of the European Crohn's and Colitis Organisation (ECCO) Congress in Barcelona, Spain

Chairperson

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Speakers

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MEETING SUMMARY

Given the progressive nature of ulcerative colitis (UC), Prof Colombel argued that effective therapy is warranted early in the disease course, especially for patients judged at a high risk of colectomy. To slow disease progression clinicians should aim for complete recovery or absence of inflammation in the gut mucosa. This goal has recently been recommended by the US Food and Drug Administration (FDA) who advised that endoscopy should be used in conjunction with histology for the assessment of mucosal healing in UC.

Considering remission in UC, Prof Feagan explained that while there is clear evidence that endoscopic remission is associated with better outcomes, challenges remain in achieving remission with current agents. Studies show utility for incorporating histopathological activity into clinical trials, but there are concerns regarding the lack of agreement among pathologists. Two newly validated indices for evaluating histologic disease activity in UC (Robarts Histopathology Index [RHI] and Nancy Histopathology Index) open the way for histopathology to be introduced in early drug development.

Prof Schreiber reviewed vedolizumab, a gut-selective α4β7 integrin antagonist recommended by the European Crohn's and Colitis Organisation (ECCO) guidelines as a first-line biologic therapy for the treatment of moderate-to-severe UC. Data from clinical trials showed that vedolizumab has the greatest efficacy in anti-tumour necrosis factor (TNF)-naïve patients and early in the disease course. Histologic healing, reported in >50% of UC patients with endoscopic remission taking vedolizumab, is likely to be a new endpoint in clinical trials. Vedolizumab has a favourable risk-benefit profile, with >77,382 patient years of post-marketing exposure worldwide.[1]

Resetting Expectations for Therapy in Ulcerative Colitis

Professor Jean-Frédéric Colombel

For a long time it has been known that UC has a variable course, with some patients displaying chronic intermittent symptoms, some chronic continuous symptoms (a type of malignant UC), some with a flat disease course at the beginning with sudden flares, and some that show no disease activity after initial flares. The Danish IBSEN study, which followed 423 UC patients for 10 years, found that 1% showed increases in symptom intensity, 6% in chronic continuous symptoms, and 37% in chronic intermittent symptoms.[2] The study revealed over half of UC patients had an unfavourable disease course that needed to be controlled.

Like Crohn's disease (CD), UC is a progressive condition. The Swiss Inflammatory Bowel Disease (IBD) Cohort study, which followed 918 UC patients, showed that in patients with disease limited to proctitis at diagnosis, 29.1% had their disease extend into left-sided colitis and 15.6% to pancolitis after a median of 9 years (Figure 1).[3]

The extent of colonic involvement in UC has implications for the severity/activity of the disease, the need and type of medication for therapy, the rates of colectomy/hospitalisation, the risk for cancer, and mortality.

Significant associations have been found between an increased width of the presacral space (a diagnostic indicator of pelvic and rectal pathology) and disease duration, with one study showing UC patients with presacral widths >16 mm had a mean disease duration of 10.5 years compared to 4.5 years for patients with widths <16 mm.[4,5] Indeed, computed tomography (CT) scans suggest presacral morphological changes arise from the proliferation of perirectal fat and fatty infiltration of the submucosal layer.[4] Other consequences of long-term inflammation include strictures, pseudopolyposis, bridging fibrosis, dysmotility, and altered colonic permeability.[4]

Several surveys indicate that the effects of UC can be underestimated, with disconnects between doctors and patients. For example, one USA survey (involving 451 UC patients and 300 gastroenterologists) revealed that 21% of patients felt their symptoms to be "completely or mostly under control" compared with 48% of physicians.[6] Once again, 42% of patients said symptoms caused disruption to daily activities compared with 17% of physicians.

In recent years, the risk of colectomy in UC has plateaued. A comparison of three cohorts from the Dutch IBDSL study showed that the rates of early colectomy decreased between the first (1991–1997) and second cohorts (1998–2005), but no further decrease was found for the third (2006–2010).[7]

Cohort studies deliver more promising news for colorectal cancer (CRC) risk. A Danish nationwide study, following 47,374 IBD patients over 30 years, showed that while CRC risk was increased for UC patients diagnosed in the 1980s, the current risk was the same as people without IBD.[8] Increased CRC risk however persists for certain subgroups of UC patients, including those who are older, have primary sclerosing cholangitis, or severe inflammation. One study showed significant correlations between colorectal neoplasia and inflammation (odds ratio [OR]: 2.54 for each one-point increase in colonoscopical inflammation scores).[9]

Taken together, such data indicate a need to 'reset' therapeutic expectations for UC. Effective therapies, said Prof Colombel, should be initiated early in the disease course, especially for patients at risk of fast progression and colectomy, with the objective of achieving and maintaining complete recovery of inflammation in the colonic mucosa long-term.

More data is available for CD than UC to demonstrate how better outcomes are achieved when biological therapies are initiated early in the disease course. For example, in CD for patients with disease duration <1 year at study entry[10,11] >70% achieve remission while for patients with disease duration >7 years at entry, only around 40% achieve remission.[12,13]

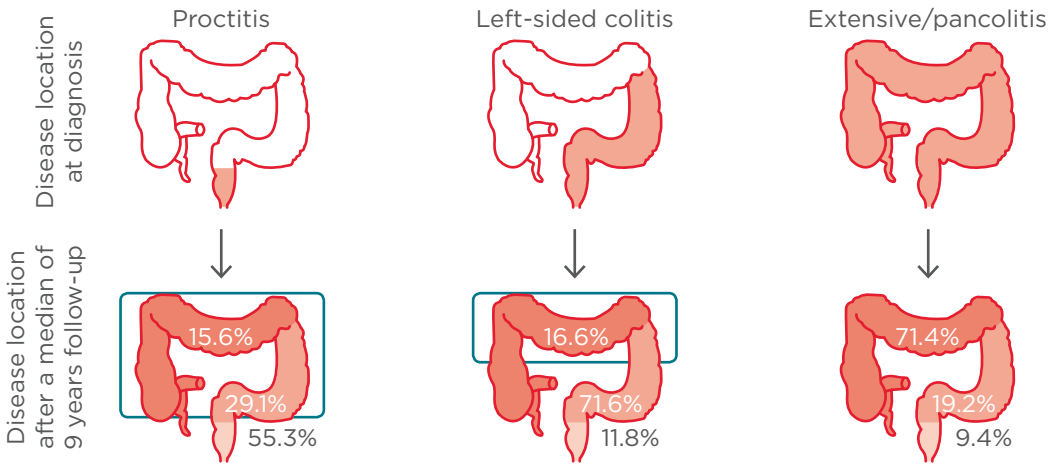

Figure 1: Ulcerative colitis as a progressive disease: Proximal extension over a median of 9 years.[3] Results from the Swiss IBD Cohort Study (N=918).
IBD: inflammatory bowel disease.

Similar studies exploring disease duration and biological therapy effectiveness are now needed in UC, Prof Colombel suggested.

The heterogeneity of UC makes it important to understand which patients are at greatest risk of colectomy, who merit receiving intensive treatment from the outset. The Norwegian IBSEN cohort study, a multivariate analysis of 464 UC patients (including 49 who underwent colectomy), revealed that the extent of disease, age, need for systemic steroids, and C-reactive protein (CRP) biomarkers/or erythrocyte sedimentation rates (ESRs), were all independently associated with colectomy risk.[14] From this, Solberg and colleagues calculated that the highest risk of colectomy occurs in a patient aged <40 years with extensive colitis, ESR/CRP ≥30, and systemic steroids at diagnosis, with a 40.1% risk of undergoing colectomy within 10 years.

Last year a literature review identified predictors for proximal disease extension (disease progressing to more extensive UC) including: delays in diagnosis >6 months, a family history of IBD, a young age at diagnosis, disease severity at onset, a need for steroids at diagnosis, a poor response to therapy (>3 relapses per year), and concurrent primary sclerosing cholangitis.[15]

The latest ECCO guidelines, published in 2012, state that the goal of UC maintenance therapy is to maintain both clinically and endoscopically defined steroid-free remission.[16] Such guidelines raise important questions of whether clinical and endoscopic remissions represent adequate treatment targets in UC. Data from an observational multicentre study by Prof Colombel shows that despite being judged as endoscopically healed (Mayo Clinic endoscopic subscores [MCSe]), around 20% of patients experience clinical symptoms, including rectal bleeding and increased stool frequency.[17] Furthermore, a chart review of 152 IBD patients judged as being in clinical remission undergoing surveillance colonoscopy showed 31% (n=47) had no signs of inflammation during endoscopy and 49% of the remaining patients (n=105) had endoscopic and/or histologic inflammation.[18] Together, such data suggests many UC patients considered to have achieved clinical remission still have evidence of active disease.

A recent observational multicentre study by Prof Colombel showed that even among UC patients with the most stringent criteria for endoscopic healing (MCSe: 0) 9% had a stool frequency score of ≥2 and 3% had rectal bleeding scores >2.[17]

Such data suggest that while endoscopical healing shows good correlations with rectal bleeding, the relationship may not be so clear for stool frequency. Indeed, discrepancies may exist between inflammation and clinical symptoms, with the patient's actual experience differing markedly from endoscopy and histology findings. Indeed, endoscopy and histology remission may not represent the final answer. To slow UC disease progression there is a need to aim for complete recovery, or absence of inflammation, in the long term in the colonic mucosa. In August 2016, the FDA recommended that in UC, "endoscopy should be

used in conjunction with histology for an assessment of mucosal healing".[19] Undoubtedly, when this new recommendation is incorporated into clinical trials it will raise the bar for IBD drugs.

Remission in Ulcerative Colitis: Has it Been Achieved and for How Long?

Professor Brian G. Feagan

Regarding the definitions for UC remission, Prof Feagan said "the devil lies in the detail". Currently, three definitions for UC remission exist: clinical, endoscopic, and histopathological. A study by Higgins et al.,[20] published in 2005, showed high correlations between clinical and endoscopic remissions in UC, leading many clinicians to believe there was no need to worry about endoscopy. This, explained Prof Feagan, was a false message.

While the two non-invasive indices correlate well with the invasive St Mark's Index (simple clinical colitis activity index [SCCAI]: 0.86; Seo index: 0.70); the correlation was not nearly so high for the Ulcerative Colitis Disease Activity Index (UCDAI) index, which takes into consideration clinical bleeding and stool frequency. One concern is that terms used in clinicians' endoscopy reports are vague (e.g. friability and granularity), which results in high inter-observer variability.

The latest ECCO statement on the diagnosis and management of UC incorporates endoscopic findings into treatment success definitions, although no endoscopic feature is specific for UC. The statement suggests: "the most useful endoscopic features of UC are considered to be continuous and confluent colonic involvement with clear demarcation of inflammation and rectal involvement".[16] The statement continued: "Endoscopic severity of UC may be best reflected by the presence of mucosal friability, spontaneous bleeding, and deep ulcerations".[16]

For the STRIDE programme, a consensus steering committee of 28 IBD specialists agreed the definition for UC remission should be a combination of clinical/patient reported outcomes (including resolution of rectal bleeding and diarrhoea/altered bowel habits) and endoscopic remission (defined as a MCSe: 0–1).[21] It is noteworthy, said Prof Feagan, how new clinical definitions of UC resolution mirror regulatory definitions. Gastroenterologists, he added, may need to justify the need for endoscopy to health payers.

Notably, STRIDE does not advocate faecal calprotectin, CRP or cross-sectional imaging as adjunctive measures of disease activity. With studies showing faecal calprotectin to be 90% sensitive and 90% specific for detecting endoscopic disease in UC, clinicians must consider whether 10% is an acceptable rate of error in making treatment decisions.

Endoscopic remission is important in UC because a large number of studies have demonstrated that the achievement of mucosal healing is associated with better outcomes. First, a Norwegian population-based cohort study of 513 UC patients (diagnosed 1990–1994) showed mucosal healing in UC was significantly associated with a low risk of future colectomy ($p=0.02$).[22] Second, an Italian study of 157 moderate-to-severe newly diagnosed UC patients showed lack of mucosal healing following corticosteroid treatment (defined by endoscopy) was associated with negative outcomes at 5 years, including colectomy ($p=0.0191$), immunosuppressant therapy ($p<0.0001$), systemic relapse ($p<0.0001$), and hospitalisation ($p=0.0001$).[23] Finally, a case-control study matching patients developing colorectal neoplasia (n=68) with two control patients from the same cohort (n=136) showed highly significant correlations between the risk of colorectal neoplasia and colonoscopical inflammation score (OR: 2.54; $p=0.001$) and histologic inflammation score (OR: 5.13; $p<0.001$).[9]

While there is clear evidence that mucosal healing is beneficial, challenges remain in achieving and maintaining remission. Pooled data from the Active UC Trials (ACT I and ACT II) showed that even among patients randomised to infliximab, 34% do not achieve a clinical response and 67% do not achieve clinical remission (Figure 2).[24] The same holds true for adalimumab, with the ULTRA I study showing at induction Week 8, 45% of patients randomised to adalimumab did not show a clinical response.[25] Furthermore, ULTRA II showed that after 54 weeks of maintenance therapy, 75% of patients randomised to adalimumab did not achieve mucosal healing.[26] Even for the most effective therapies there is room for improvement.

Step-Care, a therapeutic pyramid with 5-aminosalicyclic acid (5-ASA) at its base followed by corticosteroids, immunosuppressants, biologics, and surgery at the top, still has a place in UC.[16] 5-ASA drugs are highly effective for induction and maintenance in mild-to-moderate disease; corticosteroids are also effective for short-term

induction. However, many clinicians are now moving away from azathioprine to TNF antagonists and more recently, vedolizumab.

In CD, studies show the earlier and more frequent use of immunosuppressants and biologics to be associated with reduced rates of surgery.[27] The basic paradigm of UC treatment has for the most part remained intact. Traditionally, UC is perceived as a benign, more forgiving disease than CD, resulting in therapy delays. The SUCCESS study, which showed that UC patients benefit from combination treatments, suggests that such views are no longer appropriate.[28] SUCCESS showed that mucosal healing at Week 16 occurred in 62.8% of patients receiving the combination of infliximab/azathioprine, compared with 54.6% receiving infliximab (p=0.295) and 36.8% receiving azathioprine monotherapy (p=0.001).[28] Corticosteroid-free remission at Week 16 was achieved by 39.7% of patients receiving infliximab/azathioprine, compared with 22.1% receiving infliximab alone (p=0.017), and 23.7% receiving azathioprine alone (p=0.032).

Risk of serious infection has been a major factor limiting the use of anti-TNF-αs. The TREAT™ Registry, which followed 6,273 CD patients >5 years, showed factors predisposing individuals to serious infection, including disease activity (hazard ratio [HR]: 2.239), narcotic analgesics (HR: 1.980), prednisone (HR: 1.571), and infliximab (HR: 1.431).[29] However, if therapies help patients achieve remission and stop taking steroids, Prof Feagan explained that this was likely to offset increased risks leading to a neutral infection situation.

Turning to the future, Prof Feagan explained that US regulatory authorities are considering incorporating histopathology into remission definitions for drug approval. Evidence for histopathology comes from several studies, including the finding that in 1 in 129 patients with extensive UC, CRP levels >23 mg/L at diagnosis are predicted to have subsequent surgery (p=0.02).[30] Faecal calprotectin can also be used, with one study showing levels to be significantly lower in UC patients judged to have inactive disease compared to mild, moderate, and severe disease.[31]

Current research suggests that histopathology may prove dominant over endoscopy as a marker for prognosis. A study following 91 patients for a median of 72 months, showed that histologic remission predicted reduced rates of hospitalisation, whereas endoscopic remission did not.[32] Also, a univariate analysis of a single-centre cohort study in 418 UC patients demonstrated significant relationships between histologic inflammation and progression to advanced neoplasia.[33]

Such compelling data begs the question why histopathological activity has not already been introduced to clinical trials? Prof Feagan explained the reasons included: a lack of validated instruments, disagreement among pathologists in rating inflammation, and sampling errors.

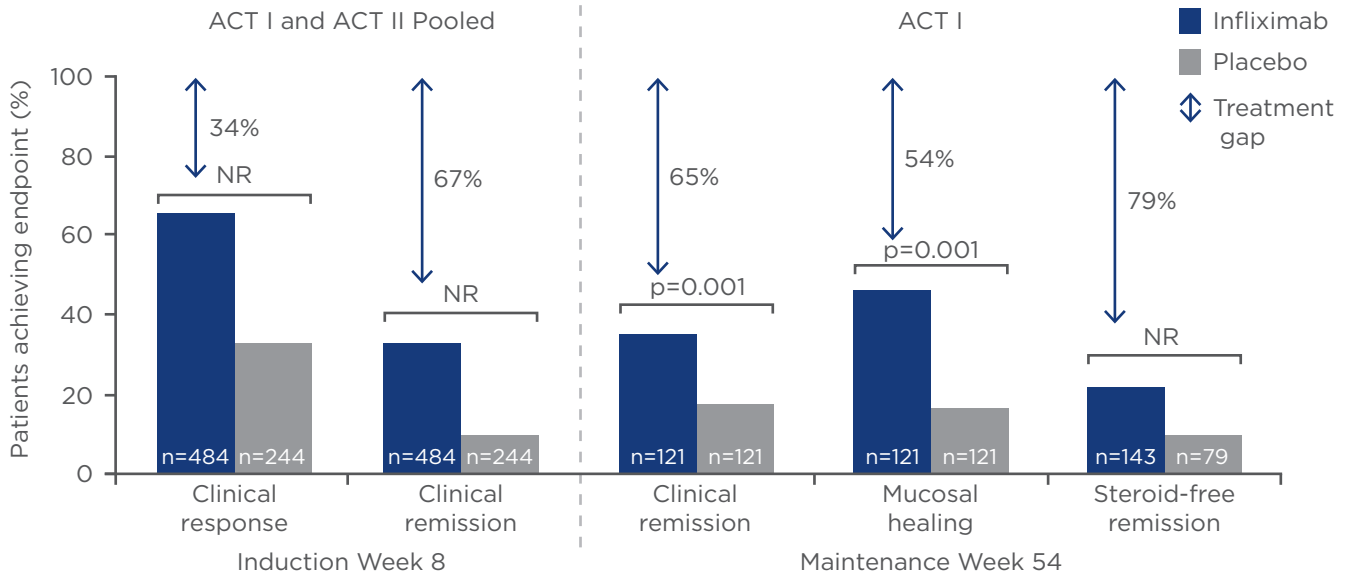

Figure 2: What is the treatment gap?[24]
Infliximab efficacy data in UC.
UC: ulcerative colitis; ACT: Active UC Trials; NR: not reported.

UC is a 'patchy' disease, making it possible to take two adjacent biopsies and achieve different results. Such variation was one of the reasons the STRIDE guidelines did not incorporate histopathology into its definition of remission.[21]

Recently, two new instruments have been developed for evaluating histologic disease activity in UC: the RHI[34] and the Nancy Histological Index.[35] Since both are well validated and sensitive to change,it is likely they will soon be introduced for early drug development. He concluded that endoscopic assessment is reliable and has prognostic value, but that histologic remission was the "new frontier" and may better predict long-term outcomes in UC.

Anti-TNF-αs are effective for the treatment of UC, but a sizeable portion of patients may not achieve adequate induction efficacy or maintain long-term clinical remission and mucosal healing.[24,26] Early intensive treatment with anti-TNF-α and immunosuppressant combination therapy may improve outcomes, but there are safety issues with their long-term use.[8,9] Efficacious and well-tolerated therapy is needed for early treatment to achieve mucosal healing of UC in the long term.

Meeting Expectations for Therapy: Do Gut-Selective Biologics Deliver?

Professor Stefan Schreiber

Starting his presentation, Prof Schreiber explained the gut-selective mechanism of action of vedolizumab. α4β7 integrin (a cell surface glycoprotein expressed on circulating B and T lymphocytes) interacts with the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the intestinal vasculature. Vedolizumab is a humanised monoclonal antibody that specifically recognises the α4β7 integrin blocking gut lymphocyte trafficking, leading to reduced intestinal inflammatory responses.[36,37] The ECCO 2016 Guidelines position vedolizumab as a first-line biologic for use in patients with moderate-to-severe UC (Figure 3).

The GEMINI 1 trial led to the strong recommendation for vedolizumab inclusion within the guidelines.[38] For the induction therapy at Week 6, a total of 106 of the 225 patients receiving vedolizumab (47.1%) and 38 of the 149 patients receiving placebo (25.5%) had a clinical response (p<0.001). A total of 38 patients receiving vedolizumab (16.9%) and 8 receiving placebo (5.4%) had clinical remission (p=0.001). Rates of mucosal healing were 40.9% (92 of 225 patients) with vedolizumab and 24.8% (37 of 149) with placebo (p=0.001). For the maintenance therapy part of the trial (52 weeks), patients who responded to vedolizumab at Week 6 were randomly assigned to continue receiving therapy every 4 (n=125) or 8 weeks (n=122) or switch to placebo (n=126). Results of maintenance at Week 52 showed 41.8% of patients who continued to receive vedolizumab every 8 weeks and 44.8% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission, compared to 15.9% who switched to placebo. The high rate of steroid-free remission was particularly noteworthy and was observed in 31.4% of patients who received vedolizumab every 8 weeks, 45.2% of those treated every 4 weeks, and 13.9% who received placebo.[38,39]

Real-world data in UC confirm the benefits with vedolizumab seen in clinical trials. A meta-analysis of studies reporting vedolizumab effectiveness over 1 year, involving 1,714 patients from 98 studies (UC: 704, CD: 1,010), showed clinical remission was achieved in 24% at Week 6, 32% at Week 14, 31% at Month 6, and 51% at Year 1.[40] Furthermore, the study, presented by Prof Schreiber at ECCO 2017 showed steroid-free remission in 14% at Week 6, 26% at Week 14, 31% at Month 6, and 48% at Month 12. He said that the data pointed to excellent maintenance capabilities for vedolizumab.

Focussing on early treatment with vedolizumab, Prof Schreiber said that there is need to select patients who do best on this treatment. Another study showed that patients with extensive colitis (E3) were more prone to colectomy than patients with non-extensive colitis (E1, E2), at all timepoints following diagnosis.[41] Treatment of early disease is therefore key to prevent complications, he argued. While there is not yet data in UC, several studies on CD indicate that disease duration is an important determinant of the chance of treatment success. Anti-TNF-α therapy is more effective started in early disease (Step-Up Top-Down,[42] SONIC,[43] GETAID[44]) than later disease (CHARM,[13] ACCENT I[12]). Such data suggests anti-TNF-α therapy should be started at the front end of the disease.

Data from GEMINI I in UC patients show anti-TNF-α naïve patients do better than anti-TNF-α failures regarding clinical responses at Week 6, and clinical remission at Week 52 for Week 6 responders.[45] Such results speaks for higher chances of success when vedolizumab is the first-choice use.

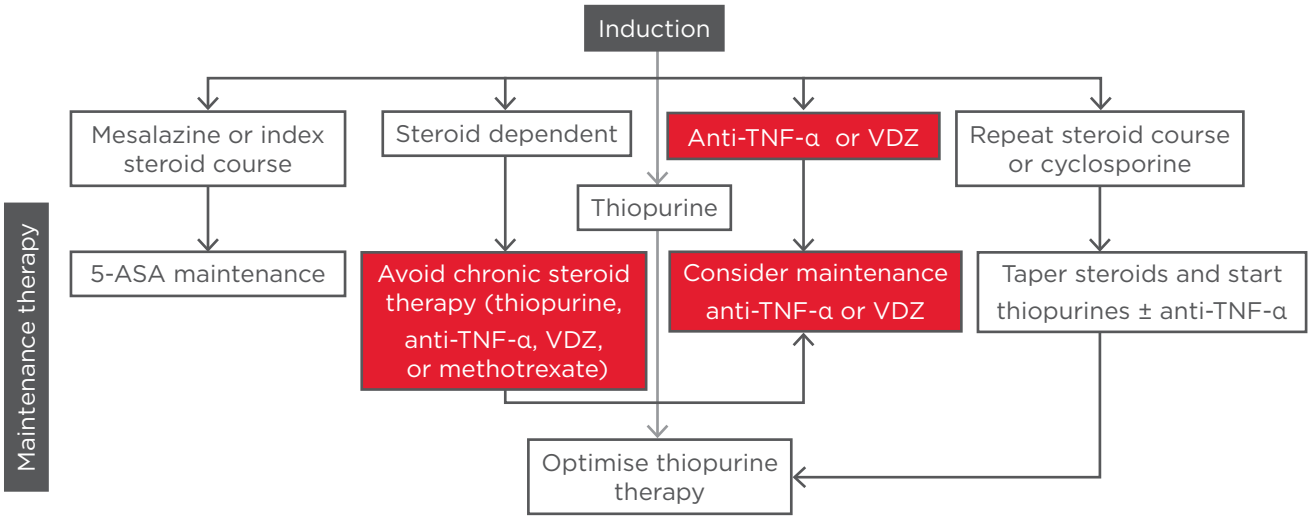

Figure 3: ECCO Guidelines 2016 for Vedolizumab – First-line biologic for moderate-to-severe UC.[51] 5-ASA: 5-aminosalicyclic acid; EL: evidence level; TNF: tumour necrosis factor; UC: ulcerative colitis; VDZ: vedolizumab.

A post hoc analysis of GEMINI I, presented at ECCO 2017,[46] showed that in patients who achieve remission at Week 14 (defined according to partial MCSe and rectal bleeding sub score of 0), sustained remission was maintained at Weeks 26, 38, and 52. Notably, anti-TNF-α naïve patients did better than those who had already experienced failure on anti-TNF-αs. Prof Schreiber said that sustained remission should be considered a major goal, because it meant the patient would be in remission at all timepoints.

Next, Prof Schreiber considered the impact of vedolizumab on complete healing of the mucosa. A post hoc analysis of GEMINI I showed while endoscopic healing (MCSe: 0 or 1) was achieved in 56% of patients receiving vedolizumab (every 4 weeks), 51.6% of patients receiving vedolizumab (every 8 weeks), and 19.8% of patients receiving placebo (who had received vedolizumab for up to 6 weeks).[38] A completely normal mucosa (MCSe: 0) was achieved in only 33.6% of patients receiving vedolizumab (every 4 weeks), 28.7% (every 8 weeks), and 8.7% receiving placebo (who had received vedolizumab for up to 6 weeks).[39]

Real-world data from the US VICTORY Consortium, presented at ECCO 2017, showed the number of prior anti-TNF-α agents used in UC was associated with incremental reductions in patients achieving mucosal healing (HR: 0.697).[47] Increased efficacy in real-world settings may relate to better patient selection and use of co-therapies, suggested Prof Schreiber. Histologic healing, requiring complete recovery of the colonic mucosa with absence of inflammation or structural changes, represents a new endpoint for UC. Potential benefits include patients being more likely to be symptom-free, and reduced risks of relapse, CRC, and surgery or hospitalisation.[32,48]

Although mucosal healing is undoubtedly an important goal, it is only a starting to be incorporated as an endpoint in clinical trials.

The latest data presented at ECCO 2017 suggest that vedolizumab delivers long-term benefits. Of the 68 patients in the GEMINI open-label extension study with data at Week 248, 98% had a clinical response and 90% were in remission.[49] Five-year safety analysis of continuous vedolizumab treatment showed no increase in the incidence of adverse events over time. Of interest, the exposure-adjusted incidence rates for infections were lower with vedolizumab than placebo, and serious infections showed the same rate with vedolizumab as placebo.[50] Prof Schreiber suggested this was likely to be due to vedolizumab bringing IBD under control, as IBD itself is a risk factor for infection. Notably, as of November 2016, vedolizumab has 77,382 patient years of post-marketing exposure worldwide.[1]

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TARGETING DISEASE PROGRESSION IN CROHN'S DISEASE: FIGHTING AN UNRELENTING ENEMY

This satellite symposium took place on 17th February 2017 as part of the European Crohn's and Colitis Organisation (ECCO) Congress in Barcelona, Spain

Chairperson

Iris Dotan[1]

Speakers

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MEETING SUMMARY

In the first presentation, Prof Panaccione considered how early treatment of Crohn's disease (CD) is key for achieving the therapeutic goals, which include symptomatic remission and mucosal healing. The latest STRIDE guidelines,[1] published in 2015, endorse endoscopic remission defined as "resolution of ulceration at ileocolonoscopy", and emphasised the need for tight monitoring of inflammation. He explored data highlighting how the ability to achieve mucosal healing decreases with increased disease duration, that benefits from mucosal healing may not be realised until the second year of treatment, and how patients who experience mucosal healing are less likely to be hospitalised and require surgery. Studies show patients do better with the 'top-down' approach, receiving anti-tumour necrosis factor (TNF) drugs early in the disease course, which has led to the introduction of a treatment algorithm suggesting patients with high-risk factors for poor prognosis should receive early 'top-down' therapy and lower-risk patients traditional 'step-up' therapy. The need for decisive early treatment to slow progression emphasises the importance of facilitating early diagnosis, and identifying patients for early biologic therapy. In the second presentation, Dr Iris Dotan explored data suggesting that optimal positioning for vedolizumab appears to be early in the course of disease. Furthermore, vedolizumab's effect on clinical remission improves over time, clinical remissions have been shown to be maintained long-term, and vedolizumab reduces rates of hospitalisation. A favourable risk-benefit profile for vedolizumab has been shown for long-term use with no increase in the incidence of adverse events in the 5-year analysis. There are now 77,382 patient-years of post-marketing exposure to vedolizumab worldwide.[2] The latest European Crohn's and Colitis Organisation (ECCO) guidelines recommend the use of vedolizumab in patients with moderate to severe localised ileocaecal and colonic CD refractory to steroids and/or anti-TNF-αs.

Slowing Progression of Crohn's Disease: Decisive Treatment for Early and Long-Term Remission

Professor Remo Panaccione

Since 1995 there has been an evolution in the management of CD, starting first with 5-aminosalacylic acid (5-ASA), steroids, and azathioprine,[3,4] then moving around the year 2000 to anti-TNF-α biologics,[5-7] in 2013 to biosimilars[8,9] and vedolizumab,[10] and finally in 2016 to ustekinumab.[11] Throughout this time surgery has remained an option in CD. With so many possible treatments, clinicians need to consider the 'patient journey' and identify patients early enough to receive the right drug at the right time.

The biologic revolution began almost 20 years ago with the approval of infliximab for moderate-to-severe CD.[6] Despite the subsequent development and approval of newer anti-TNF-αs, overall induction of remission in randomised controlled trials has remained between 30% and 50%[5,12-14] and maintenance of remission between 20% and 40%.[14-17] Such data, explained Prof Panaccione, demonstrates that therapeutic gaps still exist in treatment of inflammatory bowel disease (IBD), underlining the need for new agents.

Many important lessons have been learnt from anti-TNF-αs. These agents are generally safe (although some issues remain); antibodies are detrimental for efficacy, adequate drug levels are good, and data suggest the benefit of combination therapy (anti-TNF-α plus immunomodulators). Furthermore, paradigms have changed in the anti-TNF-α era with the recognition that treating early is beneficial, and treating beyond symptoms decreases rates of surgery.[1]

CD is a chronic progressive disease inducing cumulative structural damage. A 2011 study by Pariente et al.[18] (using Lémann scores to measure cumulative structural damage) showed that with time CD patients are more likely to develop strictures, fistulae/abscesses, and undergo surgery (Figure 1). The goal for CD is to treat early and control inflammation.

Desired outcomes differ between early and late-stage CD. For early disease, they include complete absence of symptoms, no disease progression, no complications or disability, and normal quality of life (QoL), while for late-stage disease they include stabilisation of non-inflammatory symptoms, no progression of damage or disability, and improved QoL. The difference in goals emphasises that if the early treatment window of opportunity is missed, symptomatic remission will not be achieved. This is because patients may be left with chronic abdominal pain, or functional consequences leading to chronic diarrhoea, short bowel syndrome, and/or loss of the ileocaecal valve.

The concept of early treatment of disease needs to be reinforced, said Prof Panaccione, because it is here that the greatest benefits can be derived from therapy. New data presented at ECCO 2017 suggests that the window of opportunity may in reality be months rather than years. A retrospective analysis of the Alberta IBD Consortium, undertaken by Prof Panaccione and colleagues, showed CD patients prescribed thiopurines or anti-TNF-α agents at the inflammatory stage were significantly more likely to avoid surgery compared with those initiating treatment after complications (penetrating, ileal stricturing, or stricturing) had developed.[19]

Differences in early disease biology were highlighted by a subgroup analysis of the EXTEND study showing rates of healing with adalimumab decrease with disease duration. The data showed that patients with <2 years disease had mucosal healing rates of 44%, patients with 2–4 years of disease had mucosal healing rates of 40%, and patients with ≥5 years had mucosal healing rates of 21%.[20] Such data, said Prof Panaccione, emphasises how early intervention can result in better outcomes.

The REACT trial, randomising community gastroenterology practices to conventional management or early combined immunosuppressants (anti-TNF-αs and antimetabolite), showed that the benefits of early treatment may not be realised until the second year of therapy.[21] The study, exploring whether patients achieved remission (being off steroids) at different time points, showed combined immunosuppression did not deliver symptomatic remission benefits until after Month 24 of treatment (p=0.959 at Month 6, p=0.517 at Month 12, p=0.441 at Month 18, and p=0.083 at Month 24). At 24 months, the composite of major adverse outcomes (occurrence of surgery, hospital admission, or serious disease-related complications) was 27.7% for combined immunosuppression versus 35.1% for conventional treatment (hazard ratio [HR]: 0.73, p<0.0003).

An endoscopy sub-study of the ACCENT I trial (the infliximab trial) demonstrated that success of mucosal healing can be related directly to rates of hospitalisation.[22] Among patients who achieved mucosal healing at both Week 10 and Week 54 after treatment, none required hospitalisation, compared to 18.8% of patients with mucosal healing at only one of those visits and 28% with no mucosal healing at either visit.[22]

The STRIDE treat-to-target recommendations, written in 2015 by 28 IBD specialists, define composite endpoints of clinical/patient-reported outcome remission (defined as resolution of abdominal pain and normalisation of bowel habit) and endoscopic remission (defined as resolution of ulceration at ileocolonoscopy).[1] According to STRIDE, biomarkers (C-reactive protein and calprotectin) can be considered as adjunctive measures of inflammation, but not targets for CD monitoring. While histologic remission is not currently considered a target, said Prof Panaccione, new data is anticipated later this year exploring whether surrogate markers could be used for treat-to-target beyond improvements in symptoms.

Results of the Top-Down versus Step-Up Trial, comparing early use of combined immunosuppression (infliximab and azathioprine; 'top-down') with conventional management (corticosteroids and infliximab when needed; 'step-up'), suggested initiating more intensive treatment early in disease leads to better outcomes.[23] At the end of 2 years, 73% of patients who received anti-TNF-αs as their initial therapy showed disappearance of ulcers compared with 30% receiving traditional step-up therapy (p<0.001).[23]

A subset analysis of 49 patients (taken from a study by Baert et al.[24] of 133 patients comparing the combination azathioprine and infliximab with conventional steroids) showed mucosal healing (defined as an endoscopic score of 0) after 2 years treatment predicts long-term benefits. At Year 3+4, remission occurred in 71% of patients with mucosal healing after 2 years versus 41% without (p=0.073), remission off steroids occurred in 71% with mucosal healing after 2 years versus 27% without (p=0.05), and remission off steroids and no anti-TNF-α occurred in 63% with mucosal healing at 2 years and 18% without (p<0.05). Further insights into mucosal healing are likely to come from the ongoing REACT II study (currently two-thirds enrolled), which provides escalated therapy at Week 16, 32, and 48 if patients have not shown ileocolonoscopy improvements.

The holy grail for treat-to-target, said Prof Panaccione, is to demonstrate that mucosal healing changes long-term patient outcomes. Despite the wealth of evidence for biologic therapies (mostly anti-TNF-αs), uptakes around the world remain low. A 2015 review of the epidemiology of CD, by Burisch and Munkholm, showed that earlier and more frequent use of immunomodulators/biologics in CD to be associated with reduced surgery.[25] The greatest fears for patients with CD are short and long-term side effects of therapies, with most wanting to come off therapy when they are well.

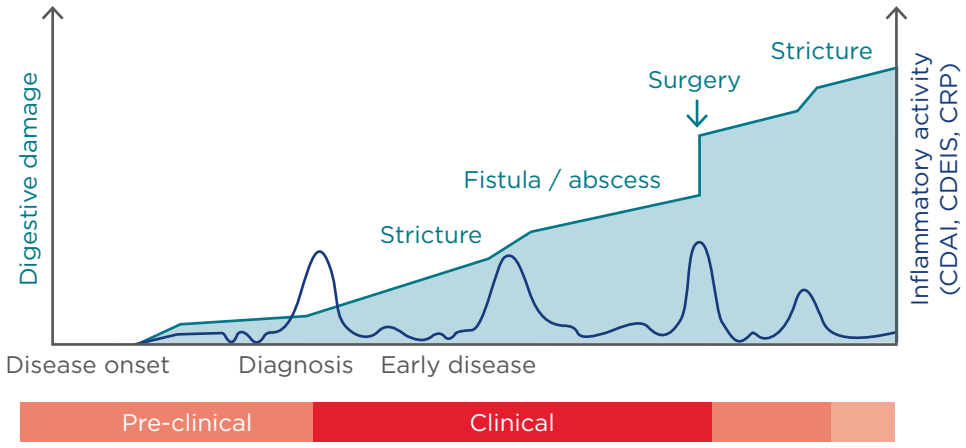

Figure 1: The progression of digestive damage and inflammatory activity in a theoretical patient with Crohn's disease.[18]

CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein.

Such concerns emphasise the importance of developing treatments that are not only safe and effective upfront, but also have long-term safety profiles.

Taking account of the possibility that long-term use of anti-TNF-αs prevents bowel damage, a 2011 treatment algorithm suggested patients with high risk factors for poor prognosis (including diagnosis at age <40 years, extensive anatomic involvement, perianal or severe rectal disease, deep ulcers, prior surgical resection, and structuring and/or penetrating behaviour) should receive early 'top-down' intervention with biologic therapy.[26] For lower-risk patients, traditional 'step-up' therapy can be used with biologic therapy introduced if they fail to respond to therapy.

A financial analogy, suggested Prof Panaccione, can be used to explain the benefits of early treatment in CD. Just as people investing early and progressively during their working lives are wealthier in retirement than those waiting until later to invest, people with CD who have anti-TNF-α treatments early do better in the long-term.

The need for decisive early treatment to slow progression emphasises the importance of facilitating early diagnosis and identifying appropriate patients for early biologic therapy. The STRIDE recommendations should be adopted for a treat-to-target approach,[1] with a rapid step-up approach being the rule, and tight monitoring of objective signs of inflammation (mucosal healing). The ultimate therapeutic goal for CD, concluded Prof Panaccione, is to return patients to normal life.

Early Use of Gut Selective Therapy in Crohn's Disease for Long-Term Remission

Doctor Iris Dotan

In the treatment of CD and ulcerative colitis (UC), there is currently a move away from the old goals of improving symptoms,[1,27] achieving a clinical remission,[1] or even a steroid-free clinical remission,[28] to new ambitions around mucosal healing[1,24,27] that ultimately achieve the goal of changing the course of disease.[1,27]

The evolving IBD environment makes it important to consider whether conventional therapies (5-ASA, steroids, thiopurines, methotrexate, and anti-TNF-α) meet the new treatment goals. Studies suggest that thiopurines and anti-TNF-α agents meet short-term end points of clinical remission, steroid-free clinical remission, and clinical and mucosal remission. It is less certain however, whether long-term goals of disease modification (involving reduction of surgical risk, disability, and damage) are significantly affected. For thiopurines there is conflicting evidence regarding reductions of surgical risk,[29] with only anti-TNF-α shown to decrease the risk of surgery in CD and UC.[30]

Studies show the 'top-down' approach, using effective therapy early in disease, delivers benefits including higher efficacy, lower disease-related complications, higher mucosal healing and decreased rates of surgery and hospitalisation.[27] However, the downsides of these treatments include higher risks of drug-related serious infections and increased costs.[27] Such consideration led the 2017 ECCO consensus on diagnosis and medical management of CD to conclude there is a "complex benefit-risk balance" for early aggressive therapeutic strategies using immunosuppressants and biologics in CD.[31]

Clinicians need to be aware that the window of opportunity is small and that in IBD early intervention is key to prevent disease progression. A longitudinal prospective observational follow-up study in 154 newly diagnosed CD patients, by Dr Dotan and colleagues, showed that by 10 months 40% had experienced disease complications (defined as progression to complicated disease, CD-related hospitalisations, or surgeries).[32] Such data, said Dr Dotan, suggest there is a need to intervene quite fast.

Vedolizumab, a gut selective anti-trafficking agent, is a newer option for the treatment of CD. Vedolizumab works by blocking α4β7 integrin (found on the surface of leukocytes), preventing them from binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) ligands (found on gut endothelial cells).[33,34]

Vedolizumab has been shown to improve outcomes in anti-TNF-α naïve patients. A post hoc analysis of the GEMINI II and GEMINI III trials showed rates of response and remission were higher in patients receiving vedolizumab as a first-line biologic than for patients who experienced prior anti-TNF-α failure (Figure 2).[35] The analysis, involving 516 anti-TNF-α naïve patients and 960 anti-TNF-α failure patients, showed for both groups that beneficial effects of vedolizumab increased with time.

A systematic meta-analysis presented at ECCO 2017 (98 studies involving 1,010 CD and 704 UC patients) further supports the concept of improvement associated with vedolizumab over time.[36] Results show pooled clinical remission was 24% at Week 6, 30% at Week 14, 23% at 6 months, and 30% at 1 year, and that pooled steroid-free clinical remission was 13% at Week 6, 25% at Week 14,23% at 6 months, and 25% at 12 months.[36]

Undoubtedly, one of the most important new goals for CD treatments is to produce mucosal healing. A promising signal for vedolizumab comes from a 2017 retrospective chart review of 32 colonoscopies undertaken in 23 CD patients enrolled in the GEMINI long-term safety study. Results in patients (who had at least 1 year of continued vedolizumab treatment) showed 44% of colonoscopies were associated with complete healing, 47% with partial healing, and 9% with no healing.[37]

Additionally, three different 'real-world' cohort studies suggest benefits for vedolizumab in achieving mucosal healing. The first study (University of Chicago, Chicago, Illinois, USA) showed mucosal healing occurred in 17% after 3 infusions;[38] the second (Mayo Clinic, Rochester, Minnesota, USA) showed mucosal healing occurred in 20%;[39] and the third study (Washington University, Seattle, Washington, USA) showed at Week 14 mucosal healing occurred in 30% and endoscopic improvement occurred in 52% (Figure 3).[40] Finally, in the VICTORY consortium study, which included 212 patients with moderate-severe CD, mucosal healing occurred in 20% of patients at Week 26, rising to 63% of patients at Week 52.[41]

What will be of vital importance, said Dr Dotan, is the ability to determine predictors of remission and mucosal healing since this helps therapies to be positioned in the clinical setting. From the US VICTORY Consortium data, it is clear patients with no prior anti-TNF-α exposure experienced more clinical remission than patients with anti-TNF-α exposure (HR: 0.40) and that patients with moderate disease experienced more clinical remission than those with severe disease (HR: 0.54).[41] Regarding mucosal healing, patients with no anti-TNF-α exposure experienced more mucosal healing than patients with anti-TNF-α exposure (HR: 0.29), and patients with moderate disease experienced more clinical remissions than those with severe disease (HR: 0.54).[41]

New data presented at ECCO 2017 reported on the effectiveness and safety of vedolizumab in CD patients who had completed GEMINI II and enrolled in the GEMINI open label extension study.

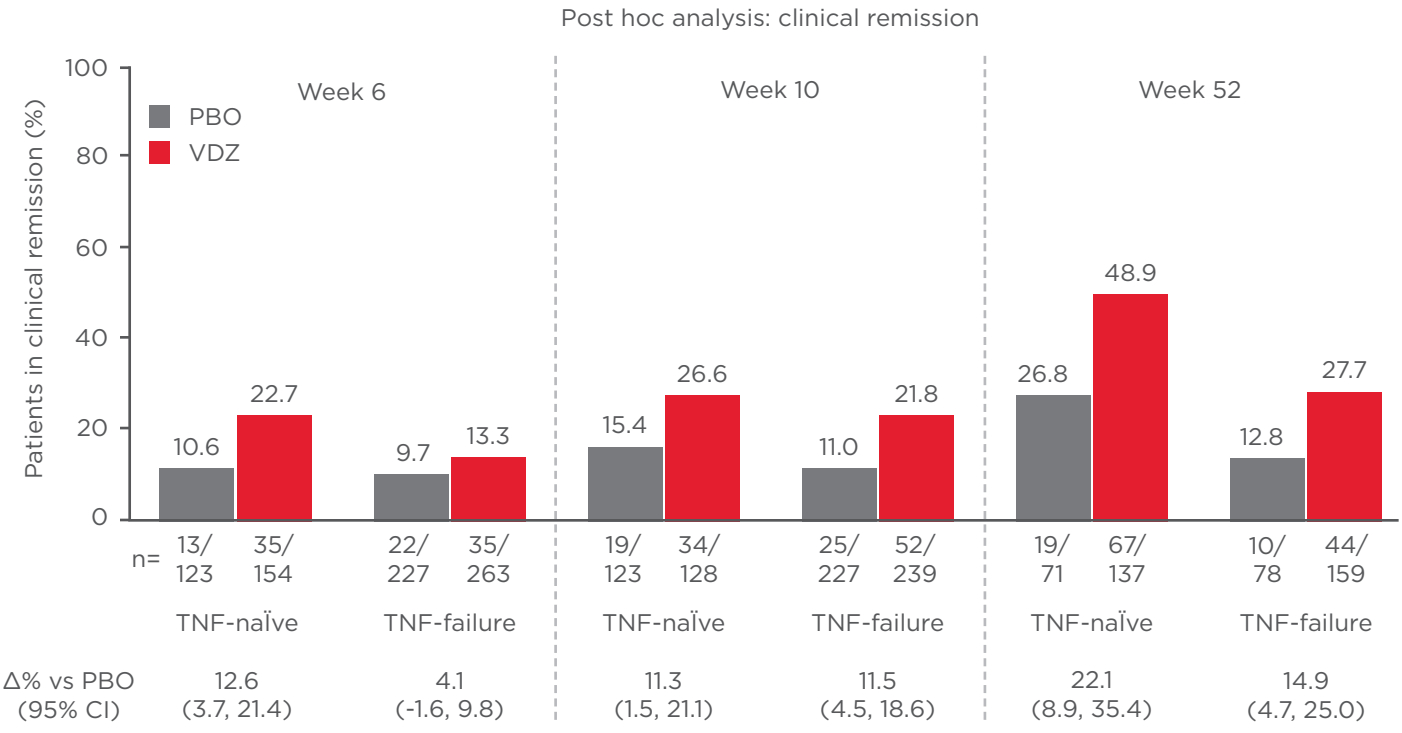

Figure 2: Biologic-naïve Patients have more prominent clinical remission (GEMINI II and III Pooled).[45]
CI: confidence interval; PBO: placebo; VDZ: vedolizumab; TNF: tumour necrosis factor.

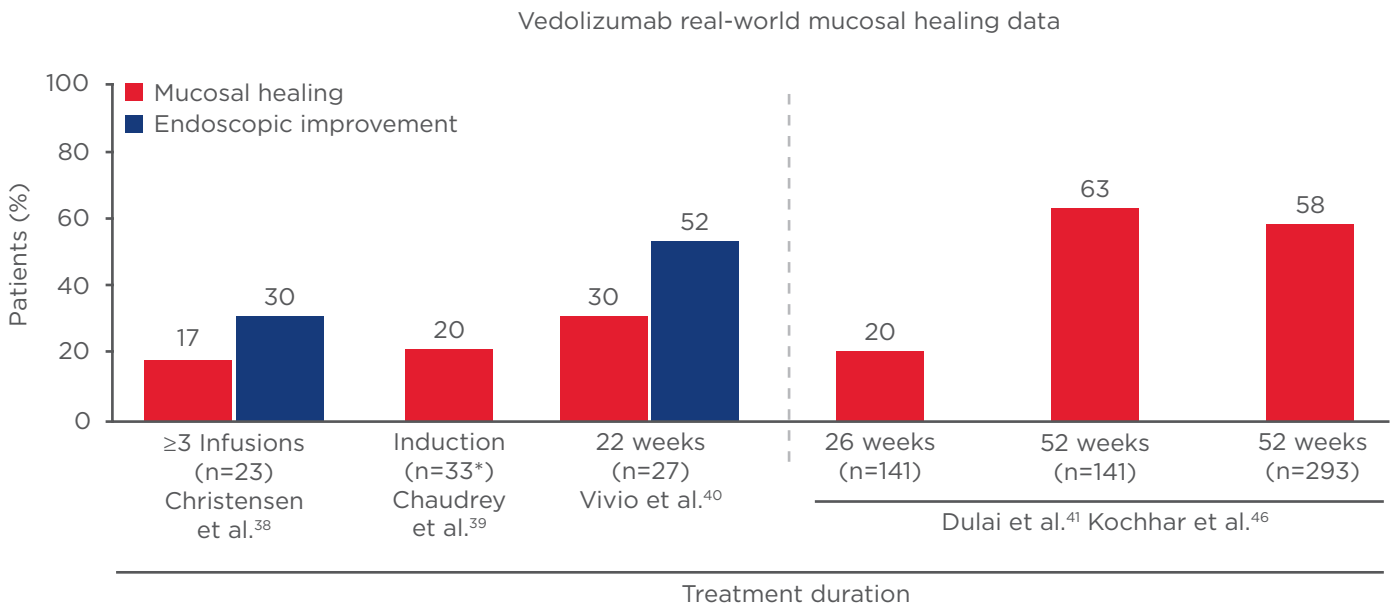

Figure 3: Mucosal Healing with Vedolizumab for Treatment of Crohn's Disease in the Real World.[40]

Data showed long-term vedolizumab therapy (˜5-years) was associated with clinical benefits including clinical response, clinical remission, and health-related QoL improvements in patients with moderate-to-severe active CD.[42]

Another study, comparing vedolizumab (n=81) versus infliximab (n=162) in biologic-naïve IBD-patients suggested that at 12 months vedolizumab was associated with a reduction (12.3%) in hospitalisation compared to infliximab (17.9%); although the result was not statistically significant.[43]

Confidence in the safety of vedolizumab was reported by Colombel et al.[44] showing no increase in the incidence of adverse events (including gastrointestinal adverse events, infections and serious infections) with long-term exposure of over 3 years. Notably, as of November 2016, vedolizumab has 77,382 patient-years of post-marketing exposure worldwide.[2]

The latest ECCO guidelines state: "decisive treatment with a potent agent ('top-down' approach) at an early stage may be preferred by the patient suffering symptoms from active disease". The guideline continues: "The therapeutic goal should be to induce clinical remission for every patient, but even at diagnosis it is essential to keep in mind how remission will be maintained after medical induction therapy".[31]

Dr Dotan concluded that vedolizumab is associated with improved remission in anti-TNF-α naïve patients, suggesting optimal positioning early in the disease course. The favourable risk-benefit profile of vedolizumab shown in the 5-year analysis supports its early and long-term use in moderate-to-severe CD. ECCO guidelines recommend the use of vedolizumab in patients with moderate-to-severe localised ileocaecal and colonic CD refractory to steroids and/or anti-TNF-αs.

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