ACHIEVING TREATMENT GOALS IN INFLAMMATORY BOWEL DISEASE: THE ROLE OF GUT-SELECTIVE THERAPY

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GUT-SELECTIVE BIOLOGIC THERAPY FOR ULCERATIVE COLITIS: LESSONS FROM SCIENCE AND PRACTICE

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MANAGEMENT OF CROHN'S DISEASE: CURRENT CONCEPTS, FUTURE DIRECTIONS

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MEETING SUMMARY

Despite major advances in the inflammatory bowel disease (IBD) treatment landscape, the management of ulcerative colitis (UC) and Crohn's disease (CD) continues to pose challenges. There is significant scope to optimise treatment of IBD, and conventional therapies may fail to meet evolving treatment goals. Induction of remission with clinical control of symptoms and maintenance of remission with long-term prevention of disease progression are important considerations for healthcare professionals. The concept of complete remission integrates clinical remission, patient-reported outcomes, and mucosal healing, a key therapeutic goal for disease modification. The anti-integrin vedolizumab has been proven to be effective in inducing and maintaining clinical remission in IBD, both first-line and in tumour necrosis factor α (TNFα)-experienced patients, and has demonstrated mucosal healing benefits in UC patients. Safety remains critical for all therapies and vedolizumab is generally well-tolerated across all age groups, including the elderly. Real-world experience with vedolizumab has shown broadly comparable outcomes to the pivotal clinical trials.

GUT-SELECTIVE BIOLOGIC THERAPY FOR ULCERATIVE COLITIS: LESSONS FROM SCIENCE AND PRACTICE

Treatment Goals in Ulcerative Colitis: Clinical Remission and Beyond

Professor Axel U. Dignass

For the past 50 years, symptom control has been the predominant treatment goal in UC. However, as the range of available therapy options for UC has expanded, disease modification has emerged as a fundamental therapeutic aim in order to prevent complications and improve patients' quality of life (QoL). Optimising care has become increasingly complex within this evolving paradigm, creating a need for validated therapeutic targets to guide healthcare professionals making treatment decisions.

The clinical course of UC can vary greatly between different patients in terms of relapse patterns and severity.[1] Although no molecular or genetic biomarkers have been demonstrated to predict the disease course, a range of clinical characteristics have been correlated with long-term disease severity and outcomes. For instance, younger age at diagnosis, the presence of extensive disease, elevated inflammatory markers, requirement for systemic corticosteroids, treatment at initial diagnosis, and persistence of rectal bleeding have been identified as predictors of complicated disease.[2-4] These clinical markers can help to guide early therapy selection in patients with UC.

Response to therapy is another key clinical indicator, and endoscopically assessed mucosal healing may be particularly important in this context. The presence of mucosal healing following 1 year of treatment has been associated with reduced colectomy risk in patients with UC.[5] In contrast, a lack of mucosal healing following initial corticosteroid therapy in patients newly diagnosed with UC appears to predict a more aggressive disease course over the next 5 years, including elevated risks for colectomy, hospitalisation, and requirement for immunosuppressant therapy.[6] The definition of remission in UC has expanded to incorporate endoscopic control, with mucosal healing as a key therapeutic goal alongside control of clinical symptoms.

Despite these developments, there is significant scope to optimise treatment. Patients with UC often do not receive ideal medical therapy – for instance, experience from a US tertiary centre suggests that inadequate prescription or dosing of immunosuppressive therapy may commonly occur in clinical practice.[7] The clinical consequences of suboptimal treatment include disabling disease relapses, the development of complications that may require surgical intervention, and increased risk of colorectal cancer. It is essential to consider the potential impact of these events on a patient's day-to-day wellbeing, as well as their ability to continue working and socialising normally and any potential fertility issues.
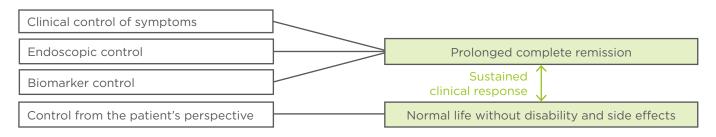
Figure 1: The evolution of treatment goals in ulcerative colitis.

Clinical practice guidelines play an important role in addressing suboptimal care, but may rapidly become outdated – for instance, the European Crohn's and Colitis Organisation (ECCO) 2012 guidelines for UC do not include newer agents such as vedolizumab,[8] as these guidelines are only updated every 4–5 years and include only evidence that has been published and thus peer-reviewed.

Enhancing patients' knowledge and engagement with therapy, for instance through shared decision-making, is increasingly recognised as a crucial way to improve outcomes, and is welcomed by patients. In a questionnaire-based study involving over 1,000 patients with IBD, 81% wanted to be actively involved in treatment decisions, and 50% expressed a need for close, equitable collaboration with their treating physician.[9] Incorporating patient-reported outcomes into therapeutic goals (Figure 1) helps to keep the patient at the centre of treatment, and may improve disease control and facilitate early detection of treatment failure.

In conclusion, the focus of treatment goals in UC now comprises long-term disease modification alongside clinical control of symptoms. The concept of complete remission, which incorporates endoscopic indicators such as mucosal healing with clinical remission (Figure 1), is central to this. Integrating patient-centred factors into treatment goals enables patients to be actively involved in their own care, and supports clinicians to understand what disease control means from each individual patient's perspective.

First-line Biologic Options for the Treatment of Ulcerative Colitis

Professor Britta Siegmund

Anti-TNFα agents, such as infliximab, adalimumab, and golimumab, and a humanised monoclonal antibody against the α4β7 integrin, vedolizumab, constitute the treatment options available for patients with UC stepping-up to biologic therapy. Efficacy, safety, and patient-related factors, such as clinical status and preference, are key considerations for clinicians selecting a first-line therapeutic strategy.

The efficacy profile of infliximab has been evaluated in two randomised, placebo-controlled studies, the Active Ulcerative Colitis Trials (ACT 1 and 2), which followed patients for up to 54 weeks (ACT 1) or 30 weeks (ACT 2).[10] Results at Week 8 demonstrated clinical remission rates of up to 40% and mucosal healing rates of approximately 60% following infliximab infusions (5 mg/kg) at Weeks 0, 2, and 6.[10] Significant improvements in patient QoL, expressed as the Inflammatory Bowel Disease Questionnaire (IBDQ) score, were also seen with infliximab compared with placebo, and were sustained up to Week 54 ($p<0.05$ for all comparisons).[11] The ACT 1 and 2 extension studies, which monitored long-term outcomes in patients continuing infliximab, showed that clinical remission was maintained in approximately 55% of patients after 3 years of infliximab treatment.[12]

Vedolizumab has also been shown to induce durable disease control. The GEMINI I study compared vedolizumab and placebo in two integrated, randomised, placebo-controlled studies that covered induction therapy up to Week 6 and maintenance therapy up to Week 52, respectively. Significantly higher rates of clinical response (47.1% versus 25.5%), clinical remission (16.9% versus 5.4%), and mucosal healing (40.9% versus 24.8%) were seen with vedolizumab compared with placebo at Week 6 ($p\leq0.001$ for all comparisons).[13] Further increases in clinical remission and mucosal healing rates were observed at Week 52 (Figure 2), and around 73% of patients completing the GEMINI I study demonstrated sustained clinical remission at 104 weeks.[14]
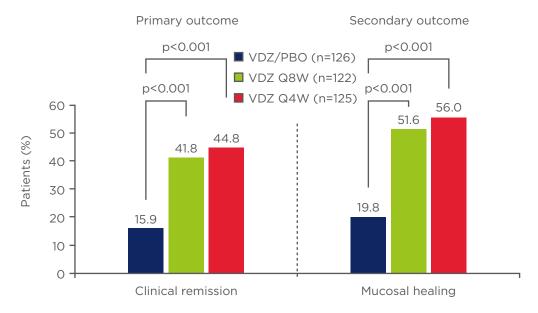
Figure 2: Clinical remission and mucosal healing rates at Week 52 with vedolizumab versus placebo.[13]
VDZ: vedolizumab; PBO: placebo; ITT: intention to treat; Q4W: every 4 weeks; Q8W: every 8 weeks.

Differentiating between infliximab and vedolizumab on the basis of their efficacy profiles is challenging, and other factors guide treatment selection in clinical practice, such as the speed of clinical response required. Infliximab demonstrates equivalent efficacy to ciclosporin over the first 7 days of treatment in patients with acute severe colitis,[15] whilst vedolizumab reduces intestinal inflammation more gradually and should not be viewed as a rescue therapy.

Safety is an essential consideration for all therapies, and a patient's specific comorbidities and their impact on the risk–benefit ratio of treatment are key factors. For instance, the risk of serious infections, such as reactivation of latent tuberculosis (TB) has been shown to increase with infliximab therapy.[16] Infections were rarely seen in the GEMINI I study,[13] and vedolizumab may be a suitable first-line option for patients at high risk of infection. All patients should be closely monitored for infection during treatment and prophylactic anti-TB therapy is indicated for patients diagnosed with latent TB during pre-treatment screening.

In addition, the relative risks and benefits of treatment should be viewed from the patient's perspective. The majority of patients want to be involved in treatment decisions,[9] and some patients, particularly those with severe disease,

may be prepared to accept greater treatment-associated risks than others.[17] A process of shared decision-making, involving patients at every step of the process, is an essential element of treatment selection for clinicians prescribing first-line biologic therapy.

Real-World Experience with Gut-Selective Therapy in Ulcerative Colitis

Doctor William J. Sandborn

Post-regulatory studies performed following the approval of vedolizumab in 2014 have demonstrated broadly comparable outcomes between the pivotal trial and clinical practice settings. In addition, real-world experience with vedolizumab has generated valuable practical insights around its clinical use, and highlighted key areas for future investigation.

Preliminary data from an analysis of patients with active moderate-to-severe UC treated in a large, multicentre, US consortium (n=59) has captured some aspects of real-world experience with vedolizumab. Progressive improvements in clinical response, clinical remission, and mucosal healing rates (Figure 3) were observed up to 30 weeks,[18] and appear to be at least equivalent to the outcomes seen in the GEMINI I study. These results are

consistent with data from a variety of other studies across the US and EU, which have demonstrated Week 14 clinical response rates of around 40–60%, and clinical remission rates of approximately 20–40%.[19-23]

A range of benefits beyond overall clinical response have been delineated by the GEMINI I study, and are supported by real-world clinical experience. For instance, as well as showing efficacy as a first-line biologic, vedolizumab has shown a consistent signal of clinical response across subgroups of patients who have received different prior therapies, including corticosteroids, immunomodulators, and anti-TNFα agents.[24] Patients in the multicentre US consortium study were frequently pretreated; the majority had received at least one prior anti-TNFα therapy (75%),[18] suggesting that vedolizumab may be effective across these groups. Vedolizumab also demonstrates efficacy across different patient age groups, including elderly individuals, in both GEMINI I and post-regulatory studies.[18,25,26]
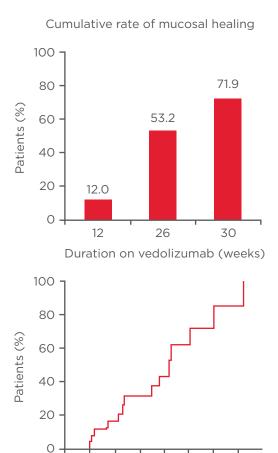
GEMINI I also demonstrated a corticosteroid-sparing effect for patients receiving vedolizumab, with 74% of patients experiencing corticosteroid dose reductions and 39% being corticosteroid-free by Week 52 of therapy, compared with 57% and 19% of the patients receiving placebo, respectively.[27] In a French observational study, 45% of patients achieving a clinical response were corticosteroid-free following 14 weeks of vedolizumab therapy.[23]

Real-world experience of vedolizumab's safety profile has been consistent with results from the clinical trials, including common adverse events involving the joints and an acneiform rash, which appeared to be self-limiting.[28] Although infectious events occurred in around 7–11% of UC patients,[18,23] no clear signal for serious or opportunistic infections or cases of progressive multifocal leukoencephalopathy (PML) have been seen. Taken together, no new safety signals have been identified by post-regulatory studies,[18] with the limitation that there are currently no data available on the safety of vedolizumab in pregnancy.

Further investigation is also needed around vedolizumab's immunogenic potential. Antibodies to vedolizumab were detected in 3–4% of patients receiving induction and maintenance therapy in the GEMINI I study,[29] but the clinical impact of these antibodies and the role of concurrent immunosuppressive therapy to prevent their formation remain incompletely understood. Other key areas requiring further study include the development of drug monitoring techniques, and combination use of vedolizumab with other medical therapies in UC. Real-world experience with vedolizumab is currently in its early stages, and continued development of this body of evidence will provide further insights around its optimal use in clinical practice.

Figure 3: Mucosal healing rates in ulcerative colitis patients treated with vedolizumab in a multicentre US consortium study.[18]

MANAGEMENT OF CROHN'S DISEASE: CURRENT CONCEPTS, FUTURE DIRECTIONS

Treatment Goals in Crohn's Disease

Doctor James O. Lindsay

As the treatment landscape in CD has transformed to include biologic therapies alongside steroids and immunomodulatory agents, treatment goals have evolved to incorporate long-term disease modification with the more traditional aim of clinical remission. Most recently, the emergence of

mechanistically novel agents such as vedolizumab and development of more affordable anti-TNFα biosimilars have expanded the range of biologic agents available for CD. However, questions remain about how clinicians can optimise their use of biologics at every stage of CD management and support patients to achieve their therapeutic aims. Selecting the right drug for the right patient is essential, and both safety and patient preference are key considerations alongside efficacy.

Although good symptomatic control is critical, clinicians should prioritise disease modification and prevention of complications in their long-term management of patients with CD. The transmural nature of intestinal inflammation in CD can lead to progressive formation of strictures and penetrating lesions necessitating surgical resection, and the possibility of stoma formation. In addition, progressive disease negatively impacts patients' overall wellbeing. In a questionnaire-based study of over 500 patients with IBD, individuals with CD reported lower health-related QoL than either patients with UC or the general population.[30]

Traditionally, clinical remission has been used to define treatment response, but clinical symptoms may not accurately reflect ongoing inflammation. For instance, the randomised SONIC trial, which compared infliximab and azathioprine combination therapy with each agent alone in biologic and immunosuppressant-naïve patients with CD, showed that around 43% of patients in clinical remission still had evidence of active mucosal disease.[31] In this context, mucosal healing has become a key therapeutic aim orientated towards disease modification. Clinical trial endpoints for IBD therapies have also evolved to reflect this shift in treatment goals, with mucosal healing and patient-focussed measures of disability becoming increasingly important considerations.

Clinicians should tailor their approach to individual patients using a range of different treatment strategies.[32] For some patients, conventional step-up care is appropriate; other patients may require a more aggressive approach, using immunomodulatory agents at diagnosis and stepping-up to a biologic if these fail. Initiating biologics at diagnosis as part of a top-down treatment strategy may be suitable for patients with severe disease. Currently, no predictive biomarkers exist to guide treatment selection in CD, although a range of clinical features have been associated with disease progression. These include the presence of extensive small bowel disease, severe upper gastrointestinal or rectal disease, complex perianal disease, deep colonic ulcers, and early development of strictures.[33-36]
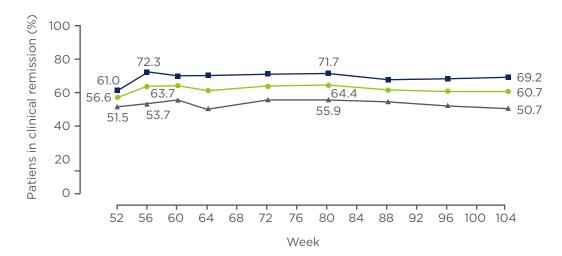
Vedolizumab GEMINI II completers

Figure 4: Clinical remission rates in the GEMINI II extension study.[39]
TNF: tumour necrosis factor.

Regardless of whether an anti-TNFα or an anti-integrin agent is selected, early treatment initiation plays a key role. For instance, 57% of patients in the SONIC trial achieved steroid-free remission at Week 26 of infliximab and azathioprine combination therapy;[37] early biologic therapy may have contributed to this high treatment response rate, as the median disease duration at trial entry was around 2 years. Durable treatment responses have also been observed with the anti-integrin agent vedolizumab, although these may develop more gradually than with anti-TNFα agents. A *post hoc* analysis of the GEMINI II study, which compared vedolizumab with placebo in patients with active moderate-to-severe CD, demonstrated that around 22% of patients who were classified as non-responders at Week 6 of the study subsequently developed a treatment response, which was maintained at 1 year.[38] The GEMINI II extension study showed that patients receiving vedolizumab remained well over the course of the subsequent 2 years, whether or not they had previously failed an anti-TNFα agent (Figure 4).[39]

The role of combination therapy at treatment initiation with vedolizumab remains to be defined. However, co-administering steroids may help to bridge the induction period. In the GEMINI II study, a higher proportion of patients treated with vedolizumab and corticosteroids achieved clinical remission at Week 6 compared with placebo or with patients treated with vedolizumab and an immunomodulator.[40] In addition to focussing on efficacy, safety is a key consideration at every stage of a patient's treatment pathway. Infection-related complications are a particular concern with biologic therapies in CD. A recent meta-analysis indicated that the risk of developing an opportunistic infection is not increased with anti-integrin use.[41] In contrast, anti-TNFα therapy carries an approximately 2-fold increased risk of opportunistic infections.[42]

To optimise care in the long term, clinicians should objectively monitor the effects of treatment in both symptomatic and asymptomatic patients. Timeframes for treatment response are drug-specific, and can take up to 12 weeks to manifest in patients receiving vedolizumab. Before switching to a different agent, efforts should be made to exclude the emergence of new complications and to optimise existing therapy, for instance through checking patient adherence to treatment and dose modification guided by therapeutic drug monitoring. A multidisciplinary 'virtual clinical' approach, where key blood results and drug doses are regularly reviewed, can help to streamline patient monitoring and facilitate optimisation of therapy.

Overcoming Treatment Challenges in Crohn's Disease

Doctor Iris Dotan

Healthcare professionals caring for patients with CD face a complex range of challenges in improving their long-term outcomes. Around 50% of these patients are candidates for biologic therapy, and selecting between different agents for first-line therapy, managing intolerance or safety issues, and switching agents in patients who do not respond or lose their initial response to therapy (defined as primary and secondary non-responders, respectively) pose key concerns.
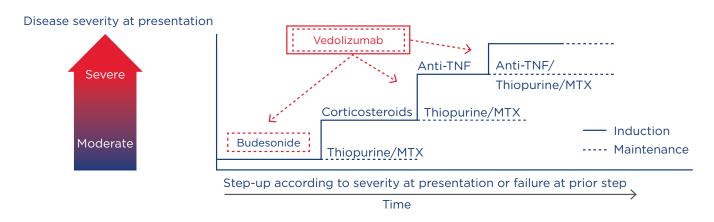

Figure 5: Potential positioning of vedolizumab in Crohn's disease.
TNF: tumour necrosis factor; MTX: methotrexate.

Real-world practical guidance can support clinicians to address these challenges in the context of their patients' long-term treatment goals.

When initiating biologic therapy, careful selection of a first-line agent is critical since treatment efficacy may decrease with subsequent lines of therapy. The GEMINI II study demonstrated higher clinical remission rates with vedolizumab in the maintenance phase of therapy in patients who had previously failed an anti-TNFα agent compared with anti-TNFα-naïve patients.[43] These findings are reflected by both a recent meta-analysis and real-world experience with vedolizumab from a US tertiary referral centre.[21,44] In a further post-regulatory study published as an abstract, clinical markers of disease activity were observed to improve as early as 2 weeks after starting vedolizumab in patients who had previously received anti-TNFα therapy.[45]

As well as being a potential option in anti-TNFα-experienced patients, re-treatment with vedolizumab appears to be safe and effective, as indicated by data from the GEMINI II extension study in patients who continued or re-started therapy following the trial's conclusion.[46] Vedolizumab also demonstrates a positive treatment effect in more aggressive phenotypes, such as fistulising disease. In patients with draining fistulae at entry to the GEMINI II study, the majority of whom had perianal disease, fistula closure rates at Week 14 were 28% in patients receiving vedolizumab induction and maintenance therapy compared with 11% in patients receiving vedolizumab induction therapy and placebo during the maintenance period.[47]

Patients who do not respond adequately to anti-TNFα therapy can be a particularly challenging group to treat. In both primary and secondary non-responders, changing to an agent in a different class may be more beneficial than an in-class switch. For instance, in a retrospective study from a European tertiary referral centre of IBD patients with primary non-response to anti-TNFα therapy (75 with CD), clinical remission without the need for drug discontinuation was seen in 31% of patients switching to another anti-TNFα and 40% of patients switching to vedolizumab. However, the need for IBD-related surgery was 63% for in-class switch and 43% for out-of-class switch.[48] In patients

with secondary non-response to anti-TNFα agents, in-class switching can result in some restoration of clinical response,[49,50] although a retrospective analysis of patients treated with a third anti-TNFα agent showed that only 33% of patients remained on treatment at 1 year.[50] This may indicate that in-class switching may not address patients' requirements for long-term therapy.

In the context of anti-TNFα non-response, an out-of-class switch to vedolizumab may be an appropriate option. Data from the randomised GEMINI III study, which evaluated vedolizumab induction therapy in patients with active moderate-to-severe CD, showed enhanced clinical response (CDAI-100) rates of 47% at Week 10 in patients who had previously failed anti-TNFα treatment.[51] Post-regulatory experience with vedolizumab further supports this concept. In a prospective, European, tertiary referral centre study in a small group of patients with treatment-refractory CD, half of whom had failed at least three previous anti-TNFα agents, clinical remission rates of 54% were observed 6 weeks after switching to vedolizumab.[19]

In addition to efficacy, monitoring and management of safety issues are of paramount importance in all patients receiving biologic therapy. Elderly patients may be at greater risk of adverse events associated with anti-TNFα therapy, primarily infectious complications.[52-54] Vedolizumab may be a relevant choice for these patients; a *post hoc* analysis of the GEMINI II study demonstrated similar Week 52 clinical remission rates and adverse event rates between patients older than 55 years and younger patients.[55] In addition, no specific safety signals for serious infections such as PML have been observed with vedolizumab, which may reflect this agent's gut-selective inhibition of leukocyte trafficking.[56]

Although the need for predictive biomarkers to guide selection of biologic therapies remains, both clinical trial data and real-world experience with these agents can guide clinicians to choose the right treatment for each patient and address specific treatment challenges. Vedolizumab is a key addition to the biologic armamentarium, and is a relevant therapeutic option across a wide spectrum of clinical presentations (Figure 5) and patient subgroups in CD.

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