Planning the Patient's Journey to Success in Crohn's Disease

This Janssen-sponsored satellite symposium took place on 3rd October 2021 as part of the United European Gastroenterology (UEG) Week Virtual 2021

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Disclosure: Vermeire has been a research supporter, principal investigator, speaker, and/or consultant for AbbVie, Abivax, Celgene, Dr Falk Pharma, Eli Lilly, Ferring, Galápagos, Genentech/Roche, Gilead, GlaxoSmithKline, Hospira, Janssen, Johnson & Johnson, MSD, Mundipharma, Pfizer, ProDigest, Progenity, Second Genome, Shire, Takeda, and Tillotts Pharma AG. Danese has been a research supporter, principal investigator, speaker, and/or consultant for AbbVie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Mundipharma, Pfizer, Sandoz, Takeda, TiGenix, UCB Pharma, and Vifor Pharma. Torres has been a research supporter, principal investigator, speaker, and/or consultant for AbbVie, Janssen, Pfizer, and Takeda.

Acknowledgements: Medical writing assistance was provided by Excerpta Medica, Amsterdam, the Netherlands.

Support: The symposium and publication of this article were funded by Janssen. The views and opinions expressed are those of the authors and not necessarily of Janssen.

Citation: EMJ Gastroenterol. 2021;10[1]:23-27.

Meeting Summary

This Janssen-sponsored satellite symposium, entitled 'Planning the patient's journey to success in Crohn's disease', took place during the United European Gastroenterology (UEG) Week Virtual 2021. The symposium focused on the considerations for the selection of the first therapy for, and the dynamic management of, Crohn's disease (CD) using treat-to-target (T2T) and tight monitoring. Séverine Vermeire presented the advantages of intervening with biologics early in the disease course by looking at key studies, and underlined the role of a T2T and tight monitoring strategy in achieving long-term disease modification. The effectiveness, durability, and safety of ustekinumab are supported by both clinical studies and real-world evidence. Silvio Danese highlighted the SEAVUE study, which showed in a head-to-head setting that ustekinumab rivalled adalimumab as a first-line treatment choice for patients newly diagnosed with CD. He also reinforced the concept that early treatment with biologics allows patients to achieve high remission rates and robust endoscopic results. Joana Torres went on to illustrate the application of these principles using a patient case-based interactive discussion with the audience. During this she focused on assessing the patient's risk for progression

or complications, determining the long-term treatment goal, and choosing the right biologic based on these factors. A key takeaway was that no treatment fits all patients and physicians should tailor therapies to the individual patient's profile and needs.

The Evolution of Dynamic Management in Crohn's Disease

Séverine Vermeire

The journey of a patient with CD starts at diagnosis. A crucial step is to identify and capture the illness early in the disease course, thereby allowing physicians to swiftly start effective treatments and set appropriate treatment targets. Each patient is unique, and physicians should tailor the treatment based on factors such as age, comorbidities, risk of infections or complications, and patient preference (personal communication, Vermeire). The current evidence indicates that early intervention in CD, defined as ≤18 months disease duration and no previous disease-modifying drugs,[1] significantly decreases inflammatory activity[2] and prevents bowel damage, disability, and the need for intestinal resections.[3] These outcomes change the natural history of the disease[3] and reduce the risk of complications, while simultaneously increasing the time in remission.[4] More specifically, clinical trials and real-world studies have shown that the early use of biologics improves clinical outcomes in both adult and paediatric patients and is accompanied by lower relapse rates and improved mucosal healing.[5]

Once a treatment regime has been established, short- and long-term treatment goals need to be determined with the aim of modifying the disease course. According to the STRIDE-II and SPIRIT consensus, the primary target for which physicians should aim in the first 3 months of therapy should be symptom control through anti-inflammatory effects of treatment. This target then evolves into deep remission between 3 months and 1 year of treatment, in which the patient should display no clinical symptoms. Beyond 1 year, the goal shifts towards mucosal healing that will ultimately lead to disease modification.[6,7] Such a T2T strategy necessitates frequent monitoring to gauge the patient's progress and to adjust therapy as needed. Along with the treatment goals, clinical and patient-reported outcome responses such as reduction in diarrhoea and cramping pain are suitable for monitoring symptom control; the assessment of deep remission is best achieved using biomarkers, including the normalisation of C-reactive protein (CRP) and faecal calprotectin (fCal) levels. Furthermore, endoscopic healing, normal quality of life (QoL), and absence of disability reflect disease modification in the long term.[6,7]

The concept of tight monitoring was adopted in the CALM study, which demonstrated that clinical decisions driven by tight monitoring of objective biomarkers paired with clinical symptoms result in superior endoscopic and clinical outcomes in CD compared with symptom-driven care only.[8,9] In addition, data from the ongoing REACT2 study indicate that the intensification of treatment based on ileocolonoscopic findings leads to fewer CD-related complications than treatment escalation based solely on symptoms.[10] The STARDUST study is the first study to investigate the benefits of T2T in patients with CD by using endoscopy at Week 16 as a decision point for the dose-adjustment of ustekinumab. Additional dose adjustments were allowed based on symptoms as well as biomarkers.[11] Compared with a symptom-driven approach, T2T numerically improved the proportion of patients achieving endoscopic response, although other outcomes such as corticosteroid-free endoscopic response, endoscopic remission, and mucosal healing were comparable.[12] Achieving mucosal healing is linked to a reduction in surgery, hospitalisations, and treatment failure,[13] while simultaneously improving long-term clinical remission rates.[14] A more advanced outcome is transmural healing, which can, crucially, be easily monitored using non-invasive intestinal ultrasound (IUS) and is increasingly recognised as an indicator of deep remission that predicts even more favourable outcomes than mucosal healing.[15] The results from the STARDUST IUS sub-study suggest that ustekinumab induced transmural healing in 11.9% of patients at Week 16, which increased over time to 24.1% by Week 48.[16]

The efficacy of ustekinumab has been analysed with a follow-up of up to 5 years in the IM-UNITI study, which demonstrated that 28.7% and 34.4% of patients receiving ustekinumab every 12 weeks and 8 weeks, respectively, were in clinical remission at Week 252.[17] Furthermore, ustekinumab improved health-related QoL and maintained its known safety profile throughout the study.[18,19] The long-term clinical efficacy of ustekinumab is not only an outcome of clinical trials but is also reflected in the real world. National cohort studies have shown that 42.1–47.7% of patients achieved clinical response and 25.7–39.4% of patients achieved clinical remission by Week 52. Importantly, over 98% of patients had prior anti-TNF experience and most of the patients in clinical response or remission were also corticosteroid-free.[20,21]

In summary, the early diagnosis and start of effective treatment are critical for the long-term outcomes in patients with CD. Appropriate treatment goals paired with a tight monitoring strategy will result in good persistence and treatment success, which ultimately changes the disease course and allows the patient to achieve full remission and excellent QoL.

Selecting the First-Line Biologic in Crohn's Disease

Silvio Danese

A crucial step in the patient's journey is the selection of a first-line treatment. Anti-TNF therapies still dominate as the first-line biologic due to their long history of use in CD. With the appearance of biologics with other mechanisms of action in recent years, head-to-head studies are becoming increasingly important for physicians to compare therapies and make informed treatment decisions for their patients. The SEAVUE study is the first head-to-head study in CD comparing biologics, in particular the efficacy and safety of ustekinumab and adalimumab.[22,23]

The patients included in the study presented with moderately-to-severely active CD and were biologic-naïve but had previously failed, or were intolerant to conventional therapies, including corticosteroids and/or immunomodulators. The median disease duration in the study was 2.62 and 2.57 years in the adalimumab and ustekinumab groups, respectively, indicating a population with relatively early disease.[23] The primary endpoint was clinical remission at Week 52, which did not differ between the ustekinumab and adalimumab treatment arms; both treatments provided clinical remission in over 60% of patients, of whom the majority were corticosteroid-free Interestingly, the kinetics of clinical remission through Week 52 showed that ustekinumab matched adalimumab at every time point, suggesting that ustekinumab has an equally rapid onset of action. Adalimumab and ustekinumab also scored similarly well regarding the other endpoints, including clinical response, endoscopic response and remission, and reduction in corticosteroid dose; however, ustekinumab exhibited a significantly higher proportion of patients maintaining clinical response at Week 52 among patients in clinical response at Week 16 compared with adalimumab (88.6% versus 78.0%). The safety profiles of both drugs were consistent with previous experience, although administration of adalimumab resulted in more injection-site reactions (10.3% versus 1%) and adverse events leading to discontinuation (11.3% versus 6.3%) than ustekinumab.[23]

Collectively, the SEAVUE data show that ustekinumab is a comparably robust option as a first-line biologic for patients with early CD who have failed conventional treatment options.

Applying New Insights to Clinical Practice

Joana Torres

The insights presented by Vermeire and Danese were translated into clinical practice using a patient case-based discussion between the expert panel and the audience, moderated by Torres, illustrating the treatment journey in the real world.

The first patient case was a 31-year-old male who presented with diarrhoea, mild abdominal pain, and fatigue. He presented with increased bowel movements (up to 4 or 5 per day) and increased CRP and fCal levels. Ileocolonoscopy revealed deep ulcers in the terminal ileum and superficial erosions in the right colon, leading to a simple endoscopic score for CD (SES-CD) score of 11.

IUS also showed severely increased bowel-wall thickness (BWT) of 7 mm in a 30 cm section of the bowel, loss of bowel-wall stratification, and fat hypertrophy. Vermeire elaborated that this patient's disease features indicate that he is highly at risk of progression towards strictures and a need for surgery in the future. Danese reiterated that the short-term treatment goal should be control of symptoms, to enable the patient to feel better. Intermediate targets would be the normalisation of biomarkers with a final goal of achieving endoscopic and mucosal healing and change in the disease course in the long run. He noted that in his clinical practice he combines non-invasive monitoring such as IUS with biomarkers to assess disease control.

The patient in this case received infliximab combined with azathioprine as a first-line treatment and initially responded well but started to lose response by Week 32. Despite treatment optimisation, he developed anti-infliximab antibodies that resulted in treatment failure. The panel debated the next line of treatment options, including adalimumab, vedolizumab, ustekinumab, or surgery. Vermeire highlighted that switching to another anti-TNF agent such as adalimumab would be unfavourable due to the development of anti-drug antibodies and that surgery was also undesirable as a large section of the bowel was affected. Vedolizumab and ustekinumab are both outstanding options to discuss with this patient, although it would be important to consider the notable durability of ustekinumab. The patient was ultimately administered ustekinumab and exhibited clinical remission, with normalised biomarkers and BWT as well as an absence of ulcers (endoscopic remission) after 8 months. This patient case underscored the importance of risk stratification and early intervention, which should be paired with monitoring to optimise treatment. Importantly, newer biologics may be accompanied by higher drug persistence and less immunogenicity, aspects that were important to consider in this clinical case.

The second patient case presented a 55-year-old female primary school teacher with a history of breast cancer that had been treated with surgery. She had recently been diagnosed with CD with ileal and pancolonic involvement with an SES-CD score of 14 and achieved an incomplete response after 2 weeks of oral corticosteroids; she was still experiencing fatigue, 4 or 5 bowel movements per day, and abdominal pain paired with elevated biomarkers. Taking the patient's age and history of cancer into consideration, the panel discussed the possible therapeutic options. Danese further stressed the significance of the durability of ustekinumab over anti-TNF therapies as well as the fact that ustekinumab can be used as monotherapy without immunosuppressants,[24] which would be more suitable for this patient given the risk of cancer. Furthermore, the SEAVUE study has shown strong response rates when treating patients early in the disease course,[23] which is also reflected in real-world studies.[25] Other studies have shown that a disease duration of ≤2 years or ≤5 years with no disease-related complications were associated with a higher probability of achieving (corticosteroid-free) clinical and endoscopic remission with ustekinumab.[26] The panel emphasised that there is no one-size-fits-all treatment and that physicians need to consider factors such as speed of onset, sustained efficacy, safety, and convenience for the patient.

Biomarkers such as CRP and fCal as well as clinical symptoms are probably accessible to all physicians to use when applying tight monitoring. Vermeire pointed out that, in her clinical practice, these are measured at baseline and Week 4 and 8 to evaluate the response to therapy. Some studies have demonstrated that early reduction of fCal <250 mg/kg predicted long-term endoscopic healing.[27] In addition, IUS is non-invasive and can complement the current clinical examination strategies, with patients showing reductions in BWT as a response to treatment as early as Week 4.[16] In combination with biomarkers, IUS may be an equivalent to endoscopy in the future, with further refinement of the technique, although endoscopy is currently still the gold standard for assessing the mucosa between 6 and 12 months after treatment. Patient education may also improve compliance to tight-monitoring strategies, which some patients may experience as a heavy burden.

In conclusion, the first-line biologic choice is crucial for determining long-term outcomes, and physicians should aim to tailor therapy to the patient's profile. Additionally, the durability, safety, convenience of administration, and improvements in QoL advocate for ustekinumab as an appealing first-choice biologic in patients

with CD. And above all, we should remember that each journey is unique: no treatment fits all patients, and physicians should tailor therapies to the individual patient's profile and needs.

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Date of preparation: October 2021
EM-69521