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New Dimensions: Exploring Recent Data and Measures in IBD

20 20 Vision in IBD

New Dimensions: Exploring Recent Data and Measures in IBD

This symposium took place on 13th February 2020, as part of the 15th Congress of the European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria

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Meeting Summary

The Janssen-sponsored symposium entitled "New dimensions: exploring recent data and measures in IBD" took place during the 15th Congress of the European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria, on 13th February 2020. Distinguished experts Prof Vermeire, Prof Armuzzi, and Prof Allez highlighted the need for improved disease control in patients with ulcerative colitis (UC), and emphasised that treatment goals may soon include histological improvement, in addition to prolonged clinical and steroid-free remission and mucosal healing. Prof Armuzzi noted that treatment goals are shifting from a focus on symptom control to measures encompassing both endoscopic and histological healing as potential targets for disease modification. Prof Allez emphasised that several histological and endoscopic measures are available that can aid in predicting inflammatory bowel disease (IBD) outcomes, and discussed how maintenance treatment with the IL-12/23 inhibitor

ustekinumab was associated with higher rates of endoscopic, histological, and histo-endoscopic mucosal healing in patients with UC, compared with placebo treatment. Prof Vermeire demonstrated how recent developments in UC management can be applied in clinical practice, using a case study to illustrate important practical points; this included an examination of when to perform biopsies and the use of histological readouts to help direct discussions about treatment plans, including the continuation, de-escalation, and cessation of treatment.

Ulcerative Colitis: New Drugs, New Targets, and Better Outcomes?

Professor Alessandro Armuzzi

UC is a chronic, progressive disorder with an unknown aetiology.[1] Few population-based cohort studies have assessed both disease course and the use of immunomodulators. However, one study examining 717 patients with cumulative exposure to medical treatment and progression to complications during a 5-year follow-up period showed that, though conditions were treated more aggressively with immunomodulators or biological therapies, disease outcomes and colectomy rates did not show significant changes.[1] Furthermore, hospitalisation and surgery rates did not decrease, indicating that UC may not have been under control after 5 years of treatment in these patients.[1] Current treatment paradigms include the use of aminosalicylates for mild disease, which can escalate to treatment with corticosteroids or aminosalicylates combined with immunomodulators, and treatment with biologics or small-molecule therapies as the disease worsens.[2-4] Patients with very severe disease may need to undergo surgery.[4]

The current therapeutic goals in UC include the rapid remission of clinical symptoms and endoscopic remission with induction therapy, prolonged clinical and endoscopic steroid-free remission, prevention of complications, optimal surgical timing, and improved patient quality of life with maintenance therapy. Recent research has put forward evidence of endoscopic healing as an appropriate treatment target that drives the course of UC.[5] This research showed that endoscopic healing was associated with improved long-term outcomes, including long-term clinical remission (odds ratio [OR]: 4.50; 95% confidence interval [CI]: 2.12–9.52), colectomy-free rate at follow-up (OR: 4.15; 95% CI: 2.53–6.81), and long-term mucosal healing (OR: 8.40; 95% CI: 3.13–22.53).[5]

A recent meta-analysis study of 2,132 patients with UC revealed that only 36% of patients showed endoscopic remission with complete abscence of symptoms, reflecting the heterogeneity of the disease.[6] Although in 2015 histological healing was not recommended as a treatment target due to insufficient evidence, accumulating evidence has shown that histological healing is associated with endoscopic healing and can help predict long-term outcomes.[7] However, endoscopic and histological remission do not completely correlate in UC outcomes; studies have shown that histological activity may be present despite clinical and endoscopic remission.[8,9] The evolving UC management landscape has shown that histological remission, though not included in the 2015 Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) recommendations, is predictive of reduced corticosteroid use and is associated with reduced risk of relapse in patients achieving endoscopic improvement and remission (Figure 1).[10-22] The future UC treatment recommendations may, therefore, soon include histological remission as an important target for optimal management.[23]

Genetic evidence links IL-23 to inflammatory disease risk.[24] Several treatments including guselkumab, brazikumab, risankizumab, and mirikizumab (all of which target the IL-23 p19 subunit), and ustekinumab (which targets the IL-23 p40 subunit) all target T-cell differentiation, resulting in a profound effect on inflammation.[24,25] For example, induction treatment with the IL-12/23 inhibitor ustekinumab, given as either a 130 mg or ~6 mg/kg intravenous (IV) dose, resulted in histo-endoscopic healing at Week 8 of treatment in patients with UC in the UNIFI study.[26]

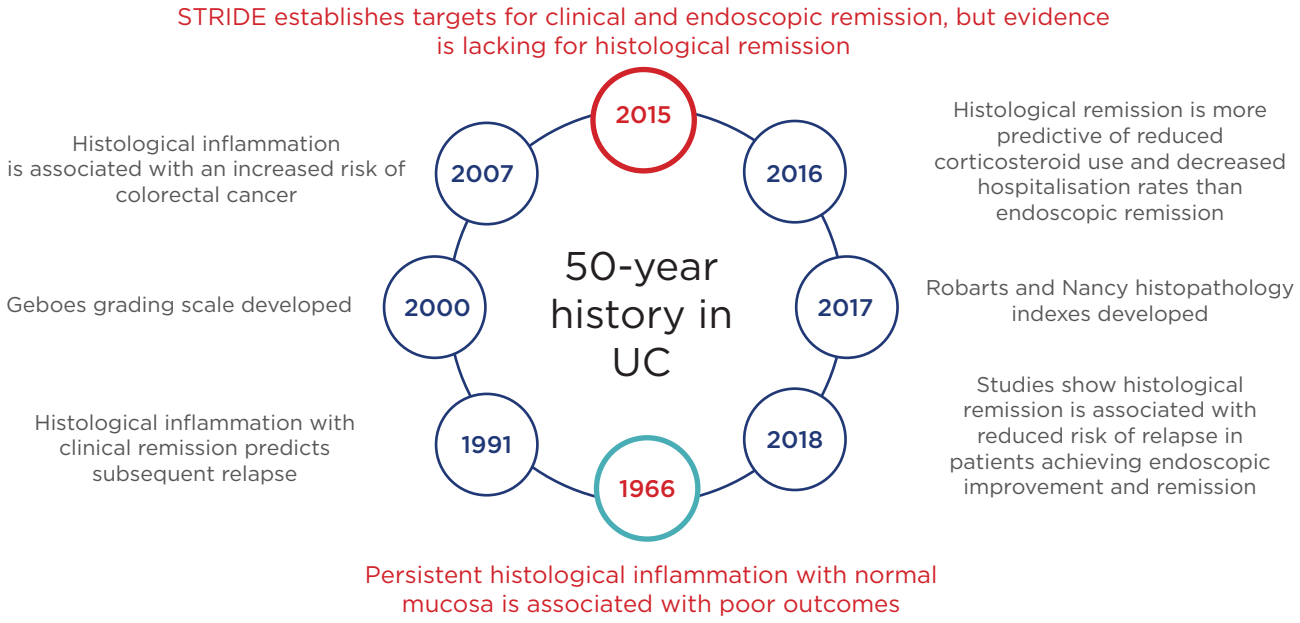

Figure 1: The history of histology in ulcerative colitis.[10-22]

STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC: ulcerative colitis.

The results of the Phase III UNIFI study, which included a novel histo-endoscopic healing outcome,[27] also showed that maintenance treatment with ustekinumab 90 mg/kg given subcutaneously (SC) every 12 or 8 weeks resulted in endoscopic and histological improvement at Week 44 of treatment, compared with placebo;[28] patients receiving ustekinumab SC during the UNIFI trial had higher rates of endoscopic improvement, histological improvement, and histo-endoscopic mucosal healing at Week 44, compared with patients receiving placebo.[28] Furthermore, symptomatic remission was sustained through Week 92 among randomised patients who continued to receive ustekinumab during the UNIFI long-term extension trial.[29] A 1-year treatment regimen with ustekinumab, including the ~6 mg/kg induction dose, was associated with a higher probability of clinical response and remission, in a network meta-analysis comparison with all advanced treatments, in patients with moderate-to-severe UC who had previously failed on one biologic therapy.[30]

In conclusion, Prof Armuzzi noted that there are still several unknowns in the treatment and management of UC, and that there are a number of remaining unmet needs in current treatment strategies. However, the evolution of therapeutic targets has now created a shift from focussing on symptom control to more objective measures of disease control, including a definition of 'complete remission' that encompasses both endoscopic and histological healing as potential targets for disease modification. Furthermore, treatment with the IL-12/23 inhibitor ustekinumab showed efficacy in induction and maintenance of histo-endoscopic mucosal healing and long-term steroid-free symptomatic remission in patients with moderate-to-severe UC.

How Good Have We Become in Predicting Long-term Outcomes in Ulcerative Colitis?

Professor Matthieu Allez

Predicting disease outcomes in patients with UC can be complicated due to individual heterogeneity, with different phenotypes and different levels of disease severity and extent, including individual responses to treatment as well as several genetic, environmental, cellular, and molecular factors.[31-33] Data from the Inflammatory Bowel Disease in South-Eastern Norway (IBSEN) cohort, which included 423 patients with UC and spanned a decade, showed that approximately

55% of patients achieved remission or had mild disease after initial high activity, while 37% of patients experienced a chronic intermittent disease course.[34] Poorly controlled UC can result in long-term consequences, including shortening of the colon and narrowing of the rectum, altered colonic activity, and anorectal dysfunction.[35] Disease activity and extent, disease course, experience with previous medications, extra-intestinal manifestations, and patient experiences should, therefore, all be considered in the UC treatment plan.

In Crohn's disease (CD), deep and extensive ulcerations during colonoscopy are indicators of an aggressive disease course; patients with deep and extensive ulcers have a significantly greater risk of colectomy and penetrating complications over time, compared with patients without lesions.[36] Deep extensive ulcerations in patients with severe endoscopic colitis and swollen mucosa in patients with moderate endoscopic colitis are also predictive factors for the outcome of intensive IV attacks of UC.[37,38] In acute severe UC, the UC endoscopic index of severity (UCEIS) at admission and faecal calprotectin (fCal) levels on Day 3 are predictive of steroid response.[39] For example, one study showed that fCal levels >1,000 µg/g on Day 3 and UCEIS levels ≥6 on admission were associated with IV corticosteroid failure and the need for medical rescue therapy or colectomy.[39]

Histological inflammation has been associated with an increased risk for colorectal neoplasia.[40] Histological activity, including deep ulceration, frequent crypt abscesses, and wide disease extent is also predictive of clinical outcomes in patients with UC.[9,41] Studies have also shown that histological normalisation is associated with relapse-free survival,[20] and that histological remission is a better predictor of steroid-use and hospitalisation than endoscopic remission.[12]

In the Phase III UNIFI trial with the IL-12/23 inhibitor ustekinumab, induction therapy with 6 mg/kg IV and maintenance therapy with 90 mg/kg SC given every 12 or 8 weeks, resulted in significantly higher rates of clinical remission at Weeks 8 and 44, respectively, compared with placebo.[27] A substantial proportion of patients with UC who were in clinical remission at maintenance baseline showed improvement at Week 44 of ustekinumab treatment, compared with placebo.[42] Furthermore, patients who were in clinical remission at maintenance baseline had better clinical outcomes than those patients who were not in clinical remission at the maintenance intiation timepoint.[42]

The results of the UNIFI study also showed that histological improvement is associated with lower disease activity and greater clinical improvement at induction Week 8. Histological improvement after induction therapy was associated with positive outcomes, including endoscopic improvement, histo-endoscopic mucosal healing, and (steroid-free) clinical remission at Week 44 of treatment (Figure 2).[27] The results of the UNIFI study also showed that histological improvement is associated with lower disease activity and greater clinical improvement at induction Week 8, and that patients who acheived histo-endoscopic healing at Week 8 were more likely to have improved outcomes at Week 44.[27] Ustekinumab treatment also promoted normalisation of colonic genes to a greater extent compared with placebo, and in patients who had achieved clinical remission at Week 44, compared with those who had not yet achieved remission.[28]

In conclusion, Prof Allez emphasised that there are several histological and endoscopic measures available in the clinic that can aid in predicting IBD outcomes. In the UNIFI study, the 90 mg SC maintenance dose of ustekinumab was associated with higher rates of endoscopic and histological healing, as well as histo-endoscopic mucosal healing in patients with UC, compared with placebo. Patients with histo-endoscopic mucosal healing after induction were also more likely to achieve more positive subsequent clinical outcomes with ustekinumab maintenance therapy than those with only endoscopic improvement at Week 44. This outcome further underscores that histo-endoscopic mucosal healing represents a broad, new clinical endpoint that is predictive of subsequent clinical outcomes.

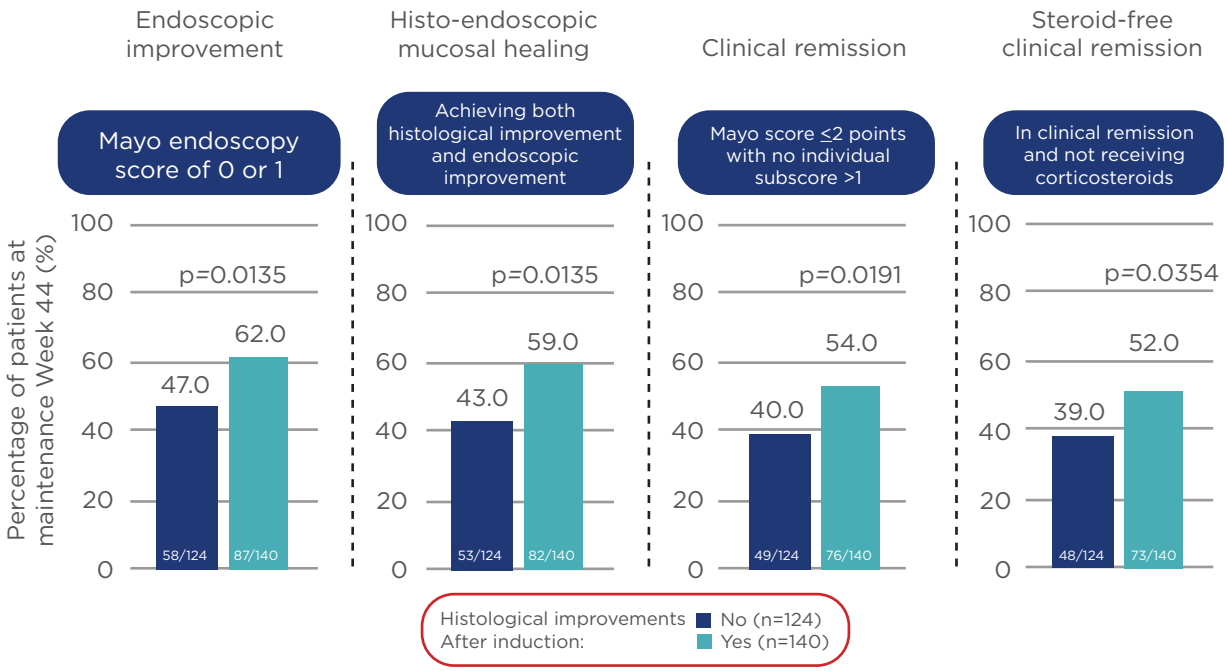

Figure 2: Histological improvement in patients with ulcerative colitis after induction therapy with ustekinumab is associated with positive outcomes at Week 44; p-values based on t-test.

Randomised patients to ustekinumab 90 mg subcutaneously every 12 or 8 weeks in the maintenance study.[27]

Is All This Applicable to Daily Clinical Practice?

Professor Séverine Vermeire

The ever-evolving principles of IBD management, including new targets, therapeutic options, and outcome measures, all represent exciting tools that can be used to help physicians optimise management of their patients. To help illustrate how the information given in the previous presentations could be applied in daily clinical practice, Prof Vermeire used the case study of a 39-year-old female patient with UC proctitis, who had been receiving oral and topical 5-aminosalycilic acid (5-ASA) and started treatment with golimumab a few years later. Two years after golimumab treatment initiation, the patient had achieved a Mayo score of 0 and showed mucosal healing on colonoscopy; however, a little more than 1 year later the patient presented with psoriasiform eczema on her face and scalp, at which point golimumab treatment was discontinued. After 3 years of only the occasional need for 5-ASA suppositories, the patient began to experience red anal blood loss and several bowel movements per day; these symptoms were not alleviated with the use of suppositories. Prof Vermeire then asked the attendees what further information might be necessary for them to make a treatment decision for the patient. More than 70% of attendees indicated that they would perform an endoscopy as well as a biopsy prior to making the next treatment decision.

Baseline assessments for optimal management include patient-reported outcomes (PRO), such as rectal bleeding and stool frequency,[43,44] and inflammatory biomarker levels, such as fCal[10,45] and C-reactive protein levels.[44,10] Patients should receive endoscopic and histological assessments, which could be assessed via the Mayo Clinic endoscopic subscore and UECIS score, and histological assessments such as the Geboes grading, Robarts histopathology index, and Nancy score. Biopsies should be performed in those who are refractory, and/or those who have severe disease.[13-15,46,47] In this patient case, a biopsy was not mandatory according to the current guidelines.

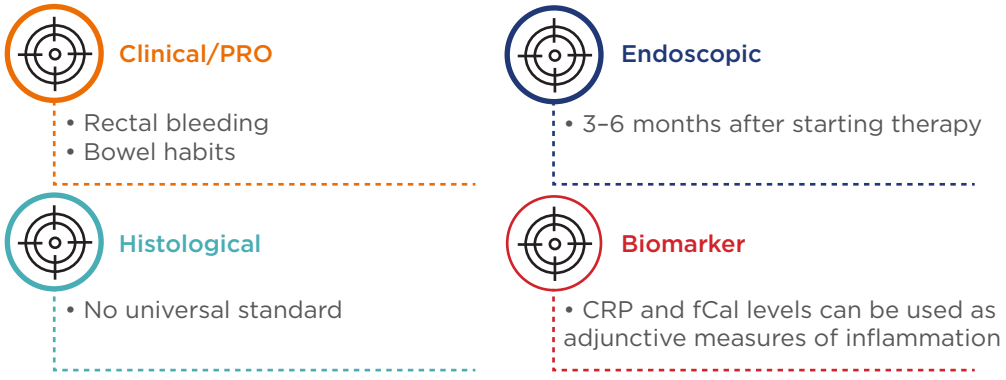

Figure 3: Follow-up assessments for optimal maintenance in ulcerative colitis management, with the goal of clinical and endoscopic steroid-free remission.[7,10,44]

CRP: C-reactive protein; fCal: faecal calprotectin; PRO: patient-reported outcomes; UC: ulcerative colitis.

Returning to the case, the PRO included red anal blood loss, 4–6 bowel movements per day, and a CRP level of <5 mg/L. Following discussion of treatment options with the patient, she started on ustekinumab therapy; the choice was made based on multiple factors including disease severity and extent, the patient's preferences and expectations, and the medication formulation and route of administration. Treatment choices should ultimately reflect these factors, focussing on the improvement of clinical, PRO, and endoscopic targets.[7,10]

Four weeks after initiating ustekinumab treatment, the patient showed improvements in blood loss and bowel movement frequency; after 8 weeks of treatment she reported only 2–3 bowel movements a day, with no urgency or blood loss and marked endoscopic improvements. Since the treatment goals of maintenance therapy include steroid-free remission (defined both clinically and endoscopically), histological and biomarker measures, as well as biopsies, can be performed to ensure optimal maintenance (Figure 3).[7,10,44] For example, histological activity may be present despite the achievement of clinical and endoscopic remission in UC and correlations between the Geboes and Mayo endoscopic subscores have been shown to be poor.[9]

Obtaining biopsies from patients may be useful, as histological improvements have previously been linked with improved clinical outcomes,[10] and evidence of histological healing may provide long-term reassurance for patients.[12] Having a histological readout may also help direct discussions about treatment plans, including the continuation, de-escalation, and cessation of treatment. Prof Vermeire concluded by sharing that, in the case of this female patient, ustekinumab treatment was given every 8 weeks, with sigmoidoscopy and bioscopies planned for later in 2020. The case study patient's plan is to de-escalate treatment to every 12 weeks when all the treatment targets have been met.

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20 20 Vision in IBD

This symposium took place on 14th February 2020, as part of the 15th Congress of The European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria

Chairperson: Subrata Ghosh[1]

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Meeting Summary

The Janssen-sponsored symposium, entitled "20 20 Vision in IBD", took place during the 15th Congress of The European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria, on 14th February 2020. Distinguished experts Prof Ghosh, Prof Atreya, and Prof Dignass illustrated the importance of the IL-12/23 pathways in inflammatory bowel disease (IBD) management, and how these pathways function in the larger picture of IBD pathogenesis. Prof Dignass presented the interim data from the STARDUST trial, the first treat-to-target, randomised clinical trial of adults with Crohn's disease (CD) using endoscopy at Week 16 as a decision point for dose adjustment of ustekinumab. The trial also included an intestinal ultrasound (IUS) substudy to examine transmural disease activity and to assess the effectiveness of ustekinumab at achieving intestinal response and remission. The interim results

showed that 75.0% and 87.0% of all patients receiving ustekinumab showed a CD activity index (CDAI) 70 response at Weeks 8 and 16, respectively. Furthermore, IUS response to ustekinumab was detected as early as Week 4 of treatment, and a clinically meaningful percentage of patients achieved transmural healing at Week 16. Prof Ghosh then highlighted how data from real-world studies mimic clinical trial results with ustekinumab in patients with CD, including patients who were previously exposed to one or more biologic treatment. The safety profile was also similar to already existing clinical trial results and the low risk of serious infections was highlighted.

Targeting the IL-12/23 Pathways in Inflammatory Bowel Disease

Professor Raja Atreya

Over the past years, the conceptual framework behind the pathogenesis of IBD has come into sharper focus. In healthy individuals, the intestinal mucosa encounters bacteria on a daily basis, but inflammation does not occur due to protection from the epithelial barrier and from cells that shield against over-reaction of the gut immune system. In patients with IBD, a multifactorial process takes place in the disease pathogenesis; there is impaired barrier function and thinning of the mucus layer, allowing luminal pathogens to enter the mucosa, activating immune cells and cytokines, and resulting in chronic inflammation.[1,2] These evolving insights into the immunopathogenesis of IBD have enabled the development of targeted therapies.[3]

The structure and function of the gut-associated immune system incorporates activation of antigen-presenting cells upon encounter of an antigen, resulting in the induction of specific effector T cells. These effector T cells egress from the mesenteric lymph nodes into the blood, and then migrate into the intestinal tissue.[4] This results in the local activation of T cells,[4] which in turn activates a cascade of dysregulated immune responses, including aberrant cytokine secretion and the differentiation and proliferation of specific effector T cells that migrate into the intestinal tissue. This results in the heightened secretion of predominantly proinflammatory cytokines by effector T cells, such as TNFα, IL-5, IL-6, IL-13, IL-17, IL-21, and IL-22, leading to inflammation and IBD development.[1,5]

In the mesenteric lymph nodes, IL-12 activates the differentiation of T cells into proinflammatory Th1 effector cells.[1,5] This differentiation can be inhibited via blockade of the IL-12/IL-12 receptor interaction, for example by the anti-IL12p40 antibody ustekinumab, that has been approved for the treatment of CD and ulcerative colitis (UC) patients.[1,5] T-cell differentiation to a proinflammatory Th17 isoform is activated by IL-6 and TGF, and IL-23 is crucial for the survival and stabilisation of these cells.[6-8] Therefore, blockade of the IL-23 pathway or the IL-23/IL-23 receptor interaction is an effective treatment strategy in IBD management.[1,5] Several therapeutic agents block these pathways, including ustekinumab, or guselkumab, risankizumab, and mirikizumab, which are currently in development for the management of CD and UC.[1,5]

Exploring New Frontiers with 'STARDUST'

Professor Axel Dignass

Treat-to-target is generally defined as a treatment strategy in which a target is preidentified and predefined, and treatment is optimised with regular monitoring and tight control until the target is achieved.[9,10] This strategy is important because it incorporates a predefined target that is achievable via optimised therapy and personalised treatment plans. In IBD management, the goal of treat-to-target strategies is to achieve remission, endoscopic improvement, or endoscopic healing as appropriate, with regular monitoring necessary to reach the predefined targets.[11] Treat-to-target goals in IBD, as defined in the 2015 STRIDE recommendations, include clinical remission, endoscopic improvement or healing, control of intestinal inflammation and normalisation of life, and avoidance of long-term bowel damage and subsequent disability.[11,12] For patients with CD, these targets include resolution of abdominal pain, normalisation of bowel habits, and absence of ulceration. For patients with UC, the targets include resolution of rectal bleeding

and normalisation of bowel habits, as well as a Mayo Endoscopic Subscore of 0 (optimal) or 1 (minimum). Cross-sectional imaging and biomarkers are not currently recommended as targets for CD or UC, but do serve as important surrogate markers for tight control of patients.[11]

Many previous and ongoing studies are focussed on tight control and treat-to-target approaches; for example, the CALM study is the first tight control study and included objective biomarkers of inflammation and clinical symptoms to drive treatment decisions.[13] This approach led to superior endoscopic and clinical outcomes in CD when compared with symptom-driven care.[13] The REACT 1 study compared the efficacy of an early combined anti-TNF treatment and an antimetabolite with that of conventional disease management for the treatment of CD.[14] The results showed that this approach was not more effective than conventional management for controlling CD, though the risk of major adverse outcomes was lower. The ongoing REACT 2 treat-to-target study is examining whether the early use of combined therapy, with an antimetabolite and adalimumab, and treatment intensification based on ileocolonoscopic findings, will lead to better outcomes and disease modification compared with treatment escalation based solely on symptoms, with deep remission as the treatment target.

The STARDUST trial is the first treat-to-target, randomised clinical trial reporting results from adults with CD using endoscopy at Week 16 as a decision point for dose adjustment of ustekinumab. This study is examining whether a maintenance strategy based on early endoscopy and regular biomarker and clinical assessments, with subsequent adjustment of treatment and predefined ultrasound examinations to assess treatment response, is more successful in obtaining endoscopic improvement than a pragmatic maintenance strategy. The first results indicate that 75.0% and 87.0% of all patients showed a CDAI 70 response at Weeks 8 and 16, respectively (Figure 1).[15] In addition, 83.0% and 83.9% of patients who were in clinical response were also in clinical remission at Weeks 8 and 16, respectively, with corresponding decreases in faecal calprotectin and C-reactive protein levels at both time points.[15]

All patients randomised to the treat-to-target arm were CDAI responders at Week 16; 58.2% of all patients showed improvements in simple endoscopic score for CD >25.0% at Week 16, with no differences between patients who were biologic-naïve and those who had prior exposure to one biologic treatment.[15] Further results showed that 36.8% of all patients had an endoscopic response and 11.4% were in clinical remission at Week 16 (Figure 2).[15]

The STARDUST trial also incorporates a substudy of IUS measures, which are comparable to MRI and CT in terms of sensitivity and specificity,[16] to examine transmural disease activity and to assess the effectiveness of ustekinumab in achieving intestinal response and remission.[17]

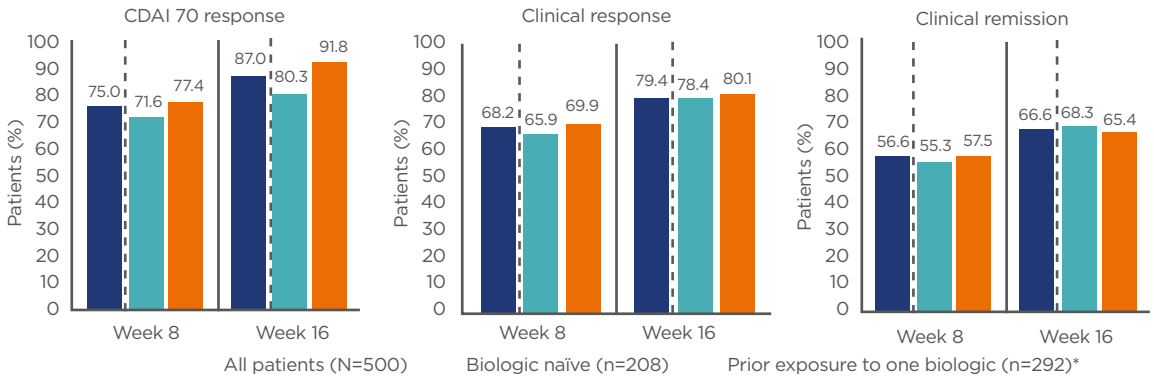

Figure 1: Crohn's disease activity index 70 response, clinical remission, and clinical response at Weeks 8 and 16 of the STARDUST trial with ustekinumab, overall and by prior exposure to biologic treatment.[15]

*77.5% of patients with prior exposure to one biologic treatment experienced treatment failure.

CDAI: Crohn's disease activity index.

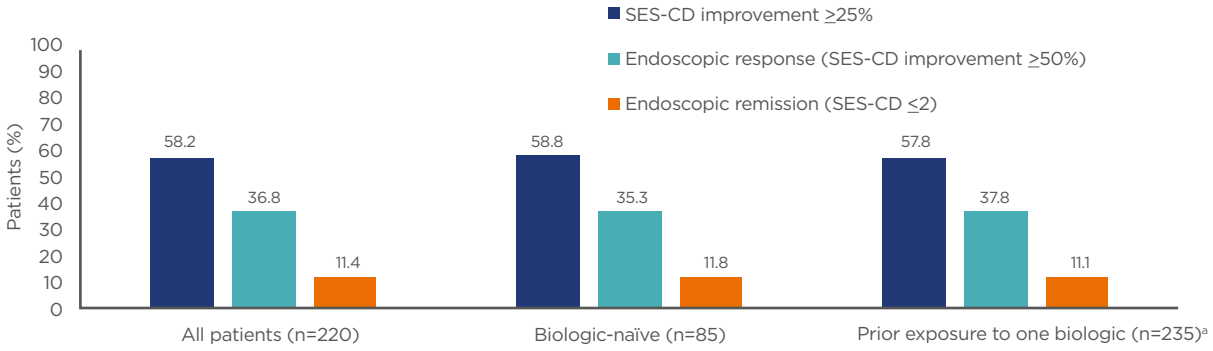

Figure 2: Endoscopic response and remission at Week 16 of ustekinumab treatment in the STARDUST trial.

Treat-to-target population: patients enrolled, treated, and randomised to the treat-to-target arm (n=220). The nonresponder imputation rule was applied for missing values or early termination.[15]

[a]77.5% of patients with prior exposure to one biologic treatment experienced treatment failure.

SES-CD: simple endoscopic score for Crohn's disease.

These measures also offer insights into a possible relationship between IUS response and change of clinical and endoscopic parameters over time.[17] Initial results from the IUS substudy show that the most affected segments were the ileum, in 66% of patients, and the colon, in 34% of patients, with increasing normalisation of bowel wall thickness over time in the most affected parts of the bowel.[17]

In conclusion, Prof Dignass emphasised that the STARDUST trial is the first interventional, multicentre, treat-to-target study in patients with CD, using endoscopy at Week 16 as a decision point for dose adjustment and exploring the use of IUS as a noninvasive tool to assess treatment response. After 16 weeks of induction treatment with ustekinumab, two-thirds of patients were in clinical remission and 37% of patients randomised to the treat-to-target arm (all CDAI 70 responders) were in endoscopic response, based on central readings. IUS response to ustekinumab was detected as early as Week 4 of treatment and a clinically meaningful percentage of patients achieved transmural healing at Week 16. These results underline the possible value of IUS as a tool to detect early response to treatment in CD. Furthermore, the safety and tolerability results were consistent with the known ustekinumab safety profile.

Sharpening Our Focus with Emerging Real-World Data

Professor Subrata Ghosh

In a discussion on the profile of ustekinumab in CD management, Prof Ghosh presented data from the IM-UNITI long-term extension trial, which show that 43.0% of patients receiving maintenance therapy with 90 mg ustekinumab every 8 weeks, and 38.0% of patients receiving the same dose of ustekinumab every 12 weeks, were in clinical remission at Week 152.[18] Among anti-TNFα-naïve patients who were randomised from baseline, 53.9% receiving the maintenance dose of ustekinumab every 8 weeks and 50.9% receiving ustekinumab every 12 weeks were in clinical remission at Week 152.[18] Furthermore, the data suggest that ustekinumab does not require concomitant treatment with immunomodulators to effectively treat patients with CD, a distinct difference when compared with anti-TNF therapies.[19]

However, it is also important to demonstrate that CD treatments are effective in the real-world setting. A national cohort study of 152 patients with CD, performed by the Belgian Inflammatory Bowel Disease Research and Development Group (BIRD), examined the long-term clinical effectiveness of ustekinumab. The results showed that, though the majority of patients had previously failed on one or more biologic

therapies, a clinically meaningful proportion of patients showed steroid-free clinical responses to treatment as early as Week 8, as well as at Weeks 16 and 52, with low occurrences of adverse events.[20]

In a Dutch national cohort study from the Initiative on Crohn's and Colitis (ICC) Registry, which included 221 patients with CD, ustekinumab efficacy was maintained through Week 52 of treatment, with increases in clinical and steroid-free remission at Weeks 24 and 52.[21] Of note, 73.0% of patients participating in the study had failed at least two prior anti-TNF therapies.[21] Similar to previous clinical trials, maintenance therapy with 90 mg ustekinumab every 8 weeks was as effective as the 12-week dose in terms of corticosteroid-free remission at Weeks 24 and 52, without the need for concomitant immunomodulator treatment.[21]

A nationwide, real-world evidence study conducted in Finland (FINUSTE),[22] consisting of a chart review from 17 centres and including 155 patients who received ustekinumab in 2017 or 2018, showed that ustekinumab treatment allowed for significant corticosteroid tapering through 1 year of treatment.[23] More than 95.0% of these patients had a treatment history of one or more previous biologic treatment at baseline.[22,23] Similarly, a Spanish Registry study (ENEIDA)[24] showed that, although 96.0% of 305 patients participating in the study previously received anti-TNFα treatment, approximately 50.0% of the patients achieved a clinical response at Weeks 8 and 14 of ustekinumab treatment. Furthermore, approximately half of the patients achieved normalisation of faecal calprotectin levels and approximately one-third achieved normalisation of C-reactive protein levels at Weeks 8 and 14 of treatment.[24] This study also revealed that the numbers of previous anti-TNFα treatments and cases of severe endoscopic activity were predictors of remission at Week 14 of treatment.[24]

An interim analysis of the Spanish SUSTAIN[25] study, which examined the long-term effectiveness and safety of ustekinumab in 331 patients with active CD in real life, showed that ustekinumab discontinuation rates were low, and that ustekinumab was effective in real-world short and long-term use. Another study of 886 patients found that patients treated with vedolizumab and ustekinumab showed higher rates of treatment persistence than patients treated with anti-TNF agents.[26] Patients treated with ustekinumab had the highest overall persistence rate.[26]

The safety profile of ustekinumab in the real world is comparable to findings from clinical trials. For example, data from the IM-UNITI LTE trial show that ustekinumab treatment resulted in low numbers of serious infections, comparable to the placebo group.[18] Studies in special populations have showed that patients with CD treated with ustekinumab have a high seroconversion rate to the seasonal trivalent influenza vaccine, in contrast to the reduced seroconversion rate seen in patients treated with adalimumab. Therefore, patients receiving ustekinumab can be effectively vaccinated with the trivalent influenza vaccine.[27] Furthermore, no severe neonatal and maternal complications occurred in female patients with IBD who were treated with ustekinumab or vedolizumab during pregnancy.[28] Additional prospective evaluations regarding safety concerns of pregnancy outcomes in patients directly exposed to ustekinumab or vedolizumab are needed.[28]

In conclusion, Prof Ghosh emphasised that the current real-world evidence demonstrates the efficacy of ustekinumab in patients with CD, including patients who were previously exposed to one or more biologic treatment. The safety profile of ustekinumab in the real world is very similar to the safety data obtained from the UNITI and IM-UNITI clinical trials. Furthermore, the efficacy of ustekinumab is similar with both combination therapy and monotherapy, and has been shown to be safe in special populations, with high seroconversion rates in patients receiving influenza vaccines and no severe neonatal or maternal complications during pregnancy.

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