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INSIDE

Entering a New Era of Patient-Reported Outcomes in Inflammatory Bowel Disease: Past, Present, and Future

This symposium took place on 16th February 2018 as part of the 13th Congress of the European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria

Chairperson: Peter Higgins[1]

Speakers: Peter Higgins,[1] Brian Feagan,[2] Peter Irving[3]

1. Higgins IBD Research Group, University of Michigan, Ann Arbor, Michigan, USA
2. Robarts Research Institute, University of Western Ontario, London, Canada
3. IBD Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK

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Meeting Summary

Considering patient-reported outcomes (PRO) for optimal disease management is pivotal in many chronic diseases, and inflammatory bowel disease (IBD) is no exception. Validated PRO that assess disease activity and reproducibly reveal how a patient functions and feels are not currently available for patients with ulcerative colitis (UC) or Crohn's disease (CD). This symposium explored how symptom-based PRO adapted from available scores and tools are evolving for effective and simple implementation in clinical practice. These instruments aim to support physicians in assessing treatment options and selection, and in the provision of long-term, meaningful benefits to patients.

Why Patient-Reported Outcomes Matter in Inflammatory Bowel Disease

Doctor Peter Higgins

Patient-Reported Outcomes Evaluate the Impact of Disease on Patients' Quality of Life Beyond Clinical Remission

Different outcome assessments, including endoscopic scores, markers of inflammation, and patient-reported symptoms, help physicians to determine the extent, severity, and impact of IBD on an individual patient. IBD symptoms are distressing for patients and burdensome on daily life, so it is important that all aspects of patient health and wellbeing are considered when assessing the individual impact of the disease. Some symptoms of IBD are tangible and measurable, for example, weight loss and fever, and others become obvious during physical examination, such as anal fistulas or abscesses. Most symptoms of IBD, however, can only be reported by patients themselves. Moreover, these symptoms can be difficult to quantify, including pain, diarrhoea, urgency of bowel movements, and fatigue.[1]

In daily clinical practice, physicians often informally enquire about the developments or changes in such symptoms. PRO measurement instruments provide structure and standardisation to these everyday assessments in the clinic. They aim to make treatment outcomes and/or disease measurements reproducible and comparable across visits and patients. Standardised, validated questionnaires evaluate the patient beyond outcomes like clinical response or remission to measure outcomes that are meaningful to patients.

The Mayo Score and Crohn's Disease Activity Index are Limited in Capturing the Impact of Disease from the Patient's Perspective

For patients with IBD, available composite measurements of disease activity include the Mayo Score and Crohn's Disease Activity Index (CDAI). These tools evaluate symptoms, clinical signs, laboratory findings, and endoscopic assessments. However, they do not capture the impact of the disease from the patient's perspective and are difficult to apply in routine clinical practice because they are complex, time-consuming, and open to bias.[2]

For example, the Mayo Score measures disease activity in patients with UC but does not assess how the disease impacts health-related quality of life (HRQoL).[2] In addition, scales for the recording of endoscopy results and rectal bleeding (RB), which are important tools in the management of patients with UC, are poorly defined. Both are recorded on a 0–3 scale, where 0 and 3 are clearly defined, but a poor definition and limited dynamic range make a score of 1 or 2 problematic, leading to bias in reporting.[3,4] For the measurement of stool frequency (SF), a lack of definition of 'normal' frequency makes the scale from 'normal' to '1–6 stools more than normal' per day subjective and open to bias.

The CDAI quantifies disease activity for patients with CD.[5] It includes objective measures and assessments of HRQoL but, importantly, it does not correlate with measures of bowel inflammation.[6] There are also methodological flaws, including low reproducibility and arbitrary cut-off points for

remission and response.[7] Furthermore, due to the wide scope of the CDAI, the score may be elevated when non-CD factors are present, such as infection or irritable bowel syndrome.[7] Despite these limitations and regulatory authorities discouraging its use,[7] CDAI has been a useful tool for identifying new effective therapies for CD patients.[8] It will continue to be a useful tool until a more accurate assessment of the effectiveness of new medications becomes available.

Health Authorities Recommend Combining Validated Patient-Reported Outcomes Instruments with Objective Inflammation Measures

Although the Mayo Score and CDAI have been widely used as endpoints in clinical trials to develop IBD therapies, health authorities have acknowledged their limitations for everyday clinical practice.[2,7,9,10] Such endpoints should not be used alone in clinical trials and should be combined with the patient's perspective to reflect real life.[7,9]

Dual measurement of disease activity using PRO instruments and objective measures of inflammation aims to ensure that improvements in disease symptoms (measured and observed) are accompanied by improvements in underlying inflammation, and vice versa.[10] In UC, these measurements usually correlate with each other. Generally speaking, PRO measures reflect how patients feel and function at the present time, whereas objective measures of inflammation predict future disease activity and clinical outcomes. The approach of combining both PRO and objective measures is critical to ensuring that all aspects of disease burden, both physical and emotional, are managed effectively and HRQoL improves as a result of therapy.

There are currently no validated PRO instruments for UC and CD and the development of validated PRO measures is a lengthy and complex process. However, Dr Higgins is a member of a consortium collaborating with patient focus groups to develop a novel five-module PRO instrument for IBD. The items, scales, and modules have been revised and refined through a series of testing and feedback. Qualitative and quantitative data have been collected and reported and are in the process of being qualified by the U.S. Food and Drug Administration (FDA) (prequalification expected in 2018). The five modules include bowel signs and symptoms, systemic symptoms, emotional impact, coping behaviours, and impact of IBD on daily life (Figure 1).

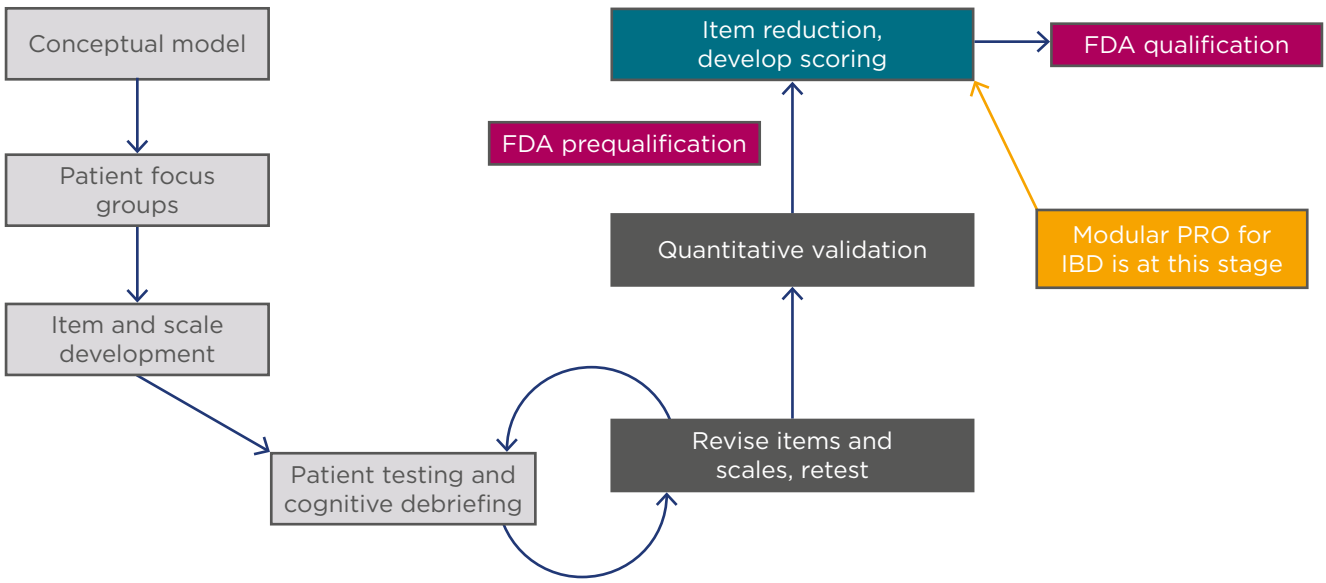

Figure 1: Process of development of a patient-reported outcomes instrument development.

FDA: U.S. Food and Drug Administration; IBD: inflammatory bowel disease; PRO: patient reported outcome.

The basis of this new PRO instrument was provided by the outcomes of the patient focus groups, which were also involved in item and scale development, and testing and retesting of the instrument. After quantitative validation and FDA prequalification, the instrument will be accessible for anyone to use. Final FDA qualification is needed before the instrument can be used in clinical trials.

Symptom-Based Patient-Reported Outcomes Instruments are Useful Tools in the Interim

Symptom-based PRO measures adapted from the Mayo Score or CDAI are considered useful until validated PRO instruments become available. In patients with UC, a two component PRO (PRO-2) combining RB and SF Mayo subscores is currently in use. PRO-2 was not developed as per FDA guidance and, therefore, is not a suitable evidential clinical trial endpoint. Nevertheless, a post-hoc analysis of a mesalazine trial in patients with UC found that the proportion of patients achieving clinical remission as defined by the study protocol had good correlation with the proportion of patients in remission as defined by PRO-2 in combination with Mayo endoscopic subscore.[11]

In CD, symptom-based PRO measures are also being used. In this scenario, PRO-2 is based on the two symptoms that are most important to patients: abdominal pain (AP) and SF.[2] In a retrospective analysis of a methotrexate trial in patients with mild-to-moderate CD, this approach was also shown to be appropriate; clinical remission rates using PRO-2 were similar to those based on a CDAI score ≤150 (the original trial endpoint).[12]

The use of symptom-based PRO measures is an important step in moving towards a more complete combination of objective and PRO endpoints. Future clinical trials in IBD will have to combine objective markers of inflammation, such as biomarkers or endoscopy results, with validated PRO instruments to encompass how the given drug improves how the patients feel and function.

Optimising Biological Therapies with Patient-Reported Outcomes in Mind

Doctor Brian Feagan

Patients are the Best Source of Information About the Impact of Their Disease

An online survey showed that physicians often underestimate disease severity and overestimate treatment effects compared with assessments completed by UC patients themselves (Figure 2).[13] This underlines the authorities' view that PRO data must originate from the patients to be considered valid.

The FDA now requires PRO instruments to include only patient-derived data. As a result, the Mayo Score and CDAI, which both collect views from patients and physicians, are no longer suitable as evidential endpoints in clinical trials.[10] Other instruments commonly used in clinical trials that require input from healthcare professionals, such as the IBD questionnaire (IBDQ), can also no longer be classified as PRO instruments. Clinical trial programmes are adapting to these changes by moving towards symptom-based PRO measures, but, for treatments already used in the clinic, previously acquired study data can only be re-evaluated against the new PRO-based definitions.

Ulcerative Colitis: The Correlation Between Patient-Reported Outcomes and Endoscopy is Reassuring

Historically, an RB subscore of 0 or 1 was included in the definition of clinical remission for the evaluation of a variety of IBD treatments, such as anti-tumour necrosis factor (TNF) therapies in patients with UC. However, with the development of newer biological therapies, the clinical remission threshold has become more stringent and now requires a RB subscore of 0.

Previously acquired clinical trial data have been reanalysed to evaluate the new PRO-based definition of clinical remission in patients with UC. A post-hoc analysis of

ULTRA-1 and ULTRA-2 trial data evaluated the relationship of RB and SF subscores with mucosal healing per endoscopy subscore in patients receiving adalimumab with moderate-to-severe UC. A RB subscore of 0 was frequently predictive of mucosal healing; however, SF was a less accurate indicator.[14]

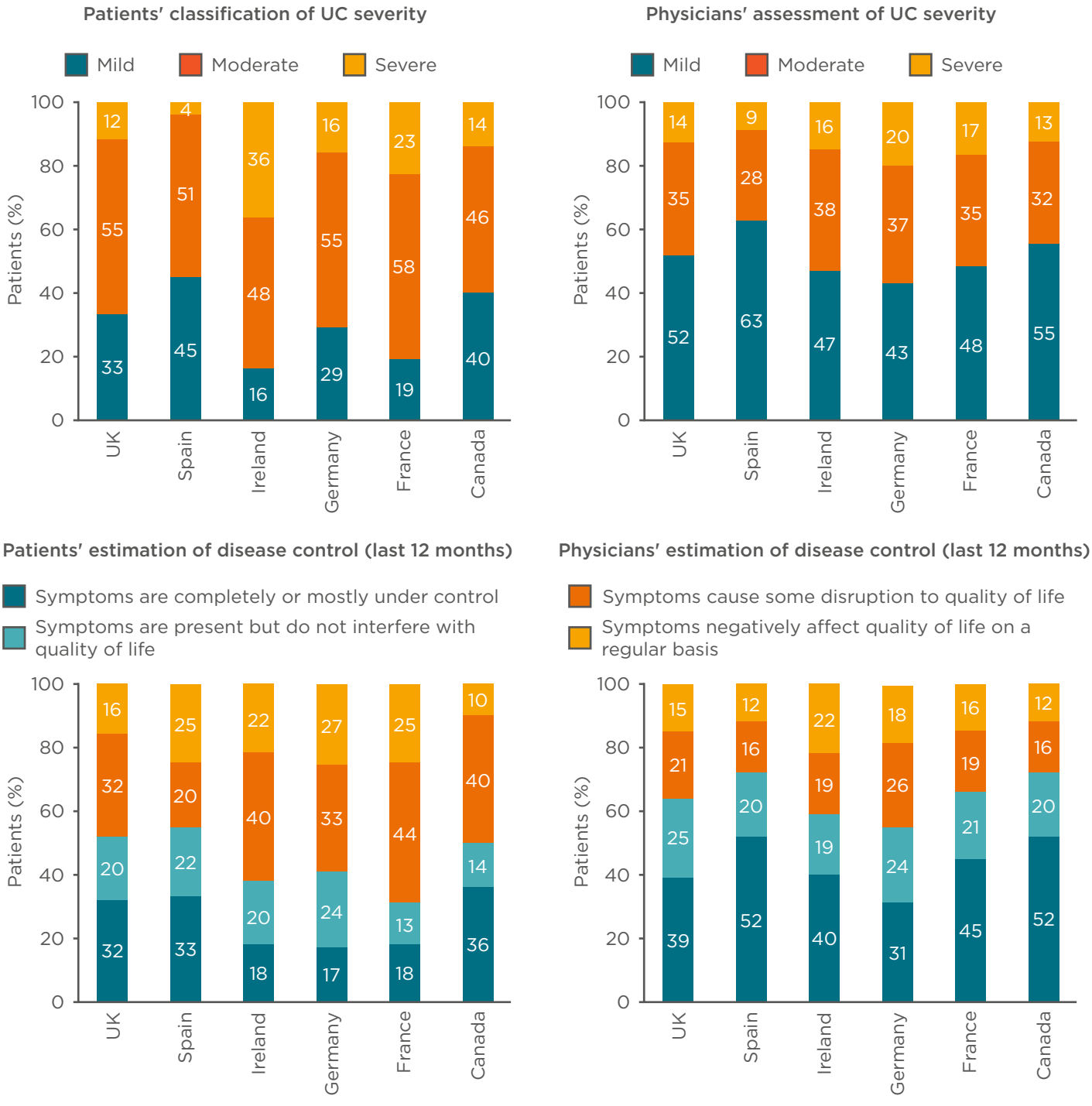

Figure 2: Online survey of patients' and physicians' perceptions of disease severity and treatment effect.

An online survey study of 775 adult patients with ulcerative colitis and 475 physicians showed that physicians systematically underestimate disease severity and overestimate treatment effect when compared with the patients' assessments.

UC: ulcerative colitis.

Adapted from Schreiber et al.[13]

A more recent post-hoc analysis of data from the GEMINI 1 trial evaluated a RB subscore of 0.[15] Within 2 weeks of starting vedolizumab therapy, 30.8% of anti-TNF-naïve patients with moderate-to-severe UC achieved complete resolution of RB (versus 18.4% with placebo). This continued to increase between Week 2 and 6, and the same trend was seen in the overall population, including patients who had previously received anti-TNF therapy.[15] This pattern was also mirrored when a composite endpoint of RB subscore of 0 and SF subscore ≤1 was used.

A RB subscore of 0 also conveyed prognostic information. Of the overall patient population with a RB subscore of 0 at Week 14, 56.7% had sustained remission at subsequent visits up to 1 year (versus 20.9% receiving placebo).[16] This effect was even more pronounced in the anti-TNF-naïve subpopulation.

Clinical trials evaluating investigational agents are also beginning to use these more stringent PRO measures. For example, the HICKORY trial[17] of etrolizumab in patients with UC refractory to or intolerant of anti-TNF therapies used the new FDA definition of PRO instruments. Data have shown that treatment with etrolizumab improved patient-reported symptoms (RB and SF) as early as Week 4, with clinically meaningful improvements in disease activity through to Week 14. Similar to the reanalysis of ULTRA-1 and 2 data,[14] improvements in RB subscores were more prominent than for SF subscores.[17]

Crohn's Disease: Convincing Study Results for Two-Component Patient-Reported Outcome Endpoints Using a Certain Cut-Off

In early trials of anti-TNF agents in patients with CD, for example the infliximab Targan et al. study[18] and the adalimumab CLASSIC study,[19] clinical remission was based on CDAI score. However, similar to UC, there has been a shift towards re-evaluating data using symptom-based PRO measures.

A recent post-hoc analysis of data from GEMINI 2, a study of vedolizumab in patients with moderately-to-severely active CD, looked at changes in AP subscore and the number of liquid or SF subscore over the 6-week induction period.[20] Similar to the UC data described above, significant improvements compared to placebo were seen as early as 2 weeks after commencing therapy. In the anti-TNF-naïve population, a 20.2% decrease from baseline in the AP subscore was reported with vedolizumab (versus 0.8% with placebo); the subscore continued to decrease to 33.7% at Week 6 (versus 12.6% with placebo). A similar, but not as prominent, decrease in AP subscore was seen in the overall population.[20]

This pattern for both populations was also observed for SF subscore, and PRO-2 (combining AP and SF subscores) showed a slightly greater effect.[20] Analysis of data to Week 52 showed that the symptom-based PRO-2 remission endpoints substantially correlated with the original trial-defined remission endpoint (CDAI ≤150) when a cut-off of AP ≤1 and SF ≤3 was used.[21]

Analyses of data from recent clinical trials of ustekinumab have confirmed that PRO-based definitions of remission deliver similar results to the original definition of CDAI <150, when PRO cut-offs of AP ≤1 and SF ≤3 were used for patients with moderate-to-severe CD who were refractory to anti-TNF treatment.[22] These cut-offs are being used in the recent and ongoing BERGAMOT trials of etrolizumab in anti-TNF-naïve and refractory patients. In the dose-finding Phase II study, there was a clear dose–response relationship for the PRO-2 definition of remission over 14 weeks of induction therapy.[23] Thus, for both UC and CD, the interim PRO-2 measures derived from the Mayo Score and the CDAI could be useful endpoints for clinical trials until new PRO instruments are defined and validated.

Continuing Development of Patient-Reported Outcomes in Inflammatory Bowel Disease

Doctor Peter Irving

Recognition of Patient-Centric Healthcare in Routine Clinical Practice

In routine clinical practice, most clinicians informally discuss PRO with their patients.

They may ask questions such as 'How many bowel movements have you been having per day?' or 'Has there been any blood in your stool?'. Although these questions are important for assessing bowel activity and are a good example of using PRO in routine clinical practice, they still do not indicate the impact of these symptoms on patients' quality of life.

Future PRO instruments should support clinicians in daily practice by standardising measurements and focussing patient consultations to gauge the impact of fluctuations in underlying disease on the symptoms that matter most to them. In addition to bowel activity, PRO instruments and measures can evaluate all aspects of patient health, including systemic symptoms, the emotional impact of disease, and coping behaviours. This, in turn, helps physicians to isolate the disease elements that patients consider to have the most impact on their daily lives.

Quality of Life is an Important Measurement of Patient-Reported Outcomes

Whereas physicians have measures at hand to evaluate inflammation in clinical practice (e.g., biomarkers or endoscopy), there are currently no PRO instruments for easy, routine use. Looking at the type of instruments used in clinical trials, there are some questionnaires assessing different aspects of quality of life that could be used in daily practice to evaluate and assess the symptoms that most concern patients. Several questionnaires and instruments have been developed to capture the impact of long-term impairment on HRQoL. For IBD, these include generic scales, such as the Short Form 36 Health Survey questionnaire and the EuroQol five-dimension scale, as well as IBD-specific scales such as the IBDQ. IBDQ32 is a HRQoL instrument with 32 items encompassing bowel symptoms, systemic symptoms, and social and emotional aspects. It has been widely used in clinical trials but has limitations, including complexity and length, as well as an associated financial and administrative burden.[2]

Change in Inflammatory Bowel Disease Questionnaire Total Score Correlates with Clinical Response but is Rarely Used in Clinical Practice

Evidence from clinical trials has shown that biological agents have a positive effect on HRQoL. In patients with CD, treatment with anti-TNF agents (adalimumab and infliximab) resulted in improvement in patients' perceptions of their disease state that was sustained with maintenance therapy, as measured by the IBDQ.[24,25] Changes in IBDQ score also had clear correlation with clinical responses to treatment in the infliximab ACT 1 and ACT 2 trials in UC.[26] Moreover, the GEMINI long-term safety study in patients with UC[27,28] and CD[29,30] showed that long-term clinical remission with continued vedolizumab treatment correlated with long-term improvements in HRQoL, regardless of prior TNF-antagonist exposure.[27-30]

Although a change in IBDQ score largely reflects patients' perceptions of their disease and matches therapeutic response, its limitations hinder its use in everyday clinical practice.[2] All questions are weighted equally, so patients' perceived importance of symptoms, such as abdominal pain and increased bowel movements,[2] is not reflected in the scoring.

Post-hoc analyses of the GEMINI 1 and 2 trials demonstrated that individual subcomponents of IBDQ had different levels of improvement in response to vedolizumab therapy. For patients with UC, improvements were reported in all subdomains as early as Week 6 and up to Week 52;[31] the greatest improvements were observed in the work or school and fatigue domains, which are particularly important to patients.[31] For patients with CD, improvements were also seen as early as Week 6, although fewer domains had sustained improvements to Week 52 than was seen for patients with UC; the greatest improvements in this cohort were observed in the sleep and fatigue domains, both of which are also important to patients.[31] It could therefore be more beneficial to study treatment effects on individual selected items of the IBDQ rather than the total score.

Table 1: Healthcare utilisation in inflammatory bowel disease patients using a patient-reported outcomes e-monitoring tool.

Healthcare utilisation	UCLA Center for Inflammatory Bowel Diseases patients (n=49) versus matched controls (n=245)	p value
Corticosteroid use	12% versus 31%	0.03
IBD-related office visits	1.7/year versus 2.2/year	0.06
Biomarker testing	1.3–3.4-times more	<0.0002
Hospitalisations	89% fewer	0.06
Emergency department visits	75% fewer	0.52

The UCLA Center for Inflammatory Bowel Diseases developed an IBD monitoring index for patient use with mobile health technologies. A comparison with matched controls revealed that UCLA Center for Inflammatory Bowel Diseases patients using this tool had lower healthcare resource utilisation than patients not using the tool.

IBD: inflammatory bowel disease; UCLA: University of California, Los Angeles, California, USA.

Adapted from van Deen et al.[35]

Inflammatory Bowel Disease-Control Questionnaire Might be Suitable for Daily Practice

The limitations of the IBDQ[2] mean there is an unmet need for a validated instrument to measure quality of life. The International Consortium for Health Outcomes Measurement (ICHOM) has developed a minimum standard set of patient-centred outcome measures for IBD. This IBD-Control Questionnaire uses a range of outcomes, including survival, disease control, and healthcare utilisation.[32,33] This tool is simple to use, freely available, quick to complete, and has been validated against the UK IBDQ, the EuroQol five-dimension scale, disease activity scores, and the Physician's Global Assessment (a rating of disease severity).[32,33]

Patient-Reported Outcomes e-Monitoring Tools May Also be Beneficial

Advances in technology are providing new possibilities for measuring PRO in clinical practice. The use of technology, such as web portals and smartphone applications, can allow data to be rapidly and efficiently accumulated. This has inspired the Center for Inflammatory Bowel Disease, University of California Los Angeles (UCLA), Los Angeles, California, USA, to develop an IBD scoring system to monitor disease activity.[34] Initial results show promise because healthcare resource utilisation outcomes were significantly improved in patients using the emonitoring tools compared with matched controls (Table 1).[35]

Conclusion

PRO measures in IBD are increasingly important for evaluating new drugs, as well as guiding treatment decisions in daily clinical practice to improve not only clinical measures of disease activity but also how patients feel and function. Until fully validated PRO instruments are available that reflect and complement objective measures of inflammation, symptom-based PRO measures derived from the Mayo Score and the CDAI are useful tools to assess treatment effect. Continued development of PRO instruments to allow for simple application in daily practice may improve delivery of value-based healthcare and, ultimately, clinical care of patients.

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Individualised Care for Crohn's Disease: Evolving Approaches for a Progressive Disease

This symposium took place on 16th February 2018 as part of the 13th Congress of the European Crohn's and Colitis Organisation (ECCO) in Vienna, Austria

Chairperson: Jean-Frédéric Colombel[1]

Speakers: Jean-Frédéric Colombel,[1] Stefan Schreiber,[2] Gert van Assche,[3] Damián García-Olmo[4]

1. Mount Sinai Hospital, New York City, New York, USA
2. Clinic of Internal Medicine, I Christian-Albrechts-University, Kiel, Germany
3. Department of Clinical and Experimental Medicine, University of Leuven, Leuven, Belgium
4. Hospital Universitario Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain

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Meeting Summary

Crohn's disease (CD) is a chronic, progressive, relapsing-remitting disorder characterised by periods of inflammatory activity occurring most commonly in the terminal ileum and colon, resulting in worsening bowel damage and increasing disability, which in turn are associated with significant impairment in quality of life (QoL). The recognition of CD as a progressive disease has shifted the goal of treatment from symptom management towards a focus on slowing disease progression,

with the aim of reducing subsequent disability and mitigating impacts on QoL. This symposium focusses on understanding the advantages and limitations of current management strategies. It addresses the full spectrum of the complexity of CD, ranging from biologic therapy for moderately-to-severely active luminal CD, to new treatment options for complex perianal fistula based on innovative stem cell approaches.

Evolving Approaches for Managing Progressive Crohn's Disease

Professor Jean-Frédéric Colombel

Since the early 2000s, it has become increasingly evident that CD is not just a relapsing-remitting disease. It is a progressive, destructive disease leading to an accumulation of bowel damage and serious, potentially disabling complications, such as strictures, abscesses, and fistulas.[1] As a result, it is essential to optimise not only treatment choices but the overall approach to the management of this disease.

Prof Colombel shared his experience working at the Mount Sinai Hospital, New York City, New York, USA in a programme called Gaining Resilience Through Transitions (GRITT), managing inflammatory bowel disease (IBD) patients in a multidisciplinary team. This initiative has enabled the provision of high-quality care for patients using telemedicine and digital health, while simultaneously decreasing costs and time-burden for treating physicians. Based on this experience, Prof Colombel proposed solutions for optimal use of therapies in Crohn's disease summarised in six key points:

- The right concept.
- The right time.
- The right drug.
- The right target.
- The right monitoring.
- The right team.

The first key point is the right concept. A key treatment goal for patients with CD should focus on slowing disease progression and damage, as well as on acute symptomatic improvement and reduction of inflammation. To do so, it is crucial to implement treatment strategies at the right time. Interventions should be initiated during the early stages of CD, wherein there is thought to be a 'window of opportunity' during which treatment might be able to alter the course of the disease to reduce eventual bowel damage and disability.[2] Several trials evaluating TNF antagonists suggest that the earlier a patient with CD is initiated with a biologic, the better the efficacy outcomes in terms of remission and response.[3-10]

Choosing the right drug for a patient is also critical. Treatments can vary from nutritional therapy, conventional corticosteroids and immunosuppressants, biologic medications, and stem cell therapy to surgery. Due to the heterogeneity of CD, the most suitable intervention or combination of interventions should be selected based on multiple factors. These include disease duration and severity, long-term risk of progression, risk:benefit ratio of the therapy, and comorbidities and complications, as well as patient preference.

The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) supports the next important point: the right target. They provide evidence and consensus-based recommendations for selecting the goals for 'treat to target' (T2T) strategies in patients with CD.[11] The IOIBD concluded that targeting clinical resolution of symptoms alone is insufficient and does not appear to significantly alter the natural course. Mucosal healing or endoscopic remission, however, provides an objective assessment of inflammation and has been shown to be associated with better outcomes in cohort studies and randomised controlled trials.[12-17] Therefore, the treatment target should be a composite endpoint involving clinical/PRO remission (defined as a resolution of abdominal pain and normalisation of bowel habit, assessed at a minimum of 3 months during active disease) and endoscopic remission (defined as resolution of ulceration, assessed at 6–9-month intervals during the active Phase).[11]

Once an intervention is in place, the right monitoring, by evaluating symptoms, inflammatory biomarkers, and endoscopy, is required to ensure tight disease control.[11,18] This allows for immediate action when the patient fails to respond to a treatment or becomes unresponsive after initial treatment success. Therapeutic drug monitoring provides the opportunity to ensure the patient is receiving the right drug at the right dosage.

Last, but not least, is the importance of the right team. A multidisciplinary healthcare team (MDT) infrastructure has been shown to improve outcomes for patients with CD. The team may include gastroenterologists, colorectal surgeons, nurses, radiologists, dieticians/nutritionists, pathologists, pharmacists, hospital management, and researchers, as well as other functions as appropriate. Depending on the stage of the patient's disease, different members of the MDT will be key.

Maximising Outcomes with Early Effective Pharmacologic Treatment of Crohn's Disease

Professor Stefan Schreiber

Prof Schreiber further emphasised the importance of initiating treatment at the right time for patients with CD. Indeed, a growing body of evidence supports the concept that initiation of treatment with disease modifying anti-IBD drugs (DMAID) during the 'window of opportunity' of early-stage CD (up to approximately 18 months from diagnosis) may change the natural progression of the disease. This, in turn, may then reduce the chances of irreversible damage and associated disability (Figure 1).[19] However, therapeutic goals during early-stage CD differ considerably compared with treatment goals for late-stage disease.

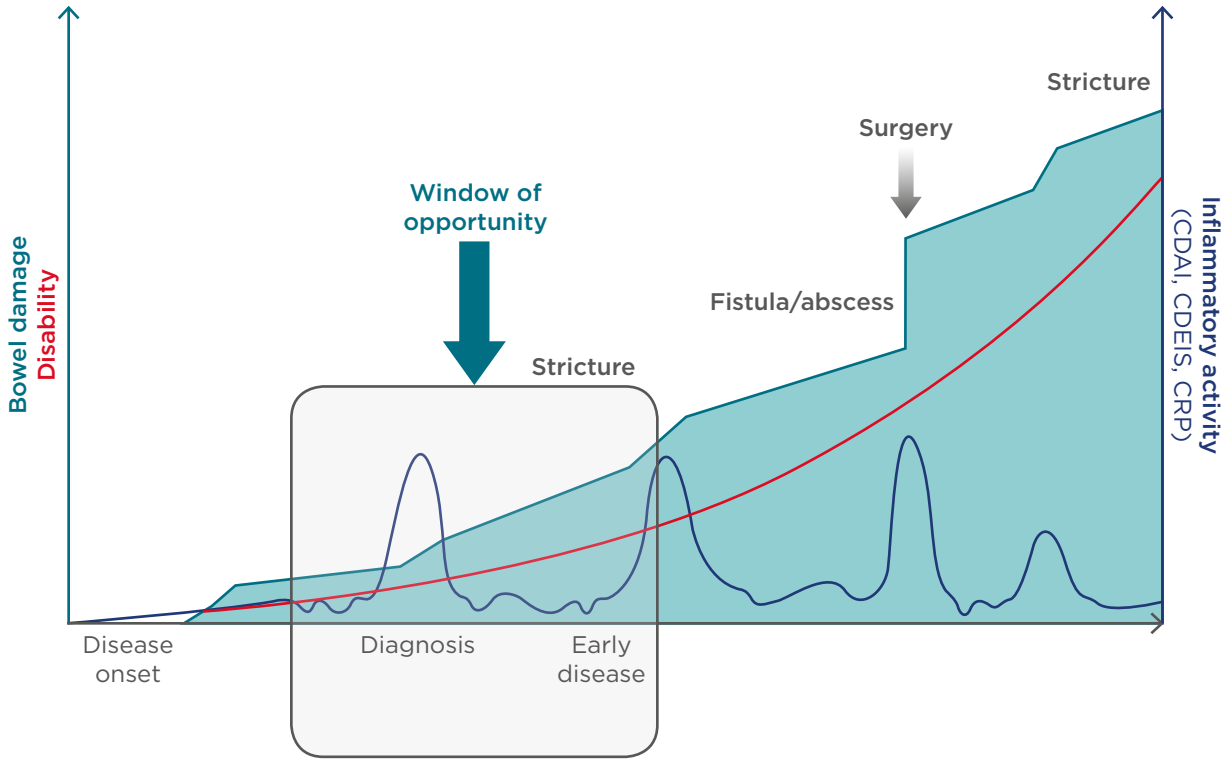

Figure 1: Early intervention and the progression of Crohn's disease.

Current evidence suggests that there may be a window of opportunity for early intervention with DMAID to change the natural progression of Crohn's disease and to prevent or reduce future complications.

CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; CRP: C reactive protein; DMAID: disease modifying anti inflammatory bowel disease drugs.

Adapted from Pariente et al.[1] and Colombel et al.[2]

During early-stage CD, an appropriate treatment goal is to attain a complete absence of symptoms, absence of complications or disability, achieving normal QoL, and ultimately slowing disease progression. However, these goals are not realistic in late stage disease, where the focus should be on stabilisation of non-inflammatory symptoms, absence of progression in bowel damage or disability, and improvement in QoL.[20]

Choosing the Appropriate Pharmacologic Treatment for Individual Patients

As previously highlighted, early interventions in appropriate patients are necessary, and, therefore, individualising treatment strategies for patients with CD is recommended. This means that patients with milder CD can be treated differently to those with more aggressive, severe CD. In mild CD, there is a space to consider the 'step up' approach to avoid unnecessary immunosuppression and adverse events (AE). Conversely, in patients with more aggressive and rapidly progressing disease, a 'top down' approach using intensive therapy at an earlier stage to avoid future complications may be considered.[19]

To aid physicians with rapid decision making, identification of the patients in whom early intensive therapy is appropriate is critical. Recognising the prognostic factors for disease progression helps to identify those patients. As part of the IBD Ahead 2014 educational programme, a panel of IBD experts from 32 countries worldwide identified several prognostic factors for disease progression in CD, including ileal disease location, upper gastrointestinal involvement and extraintestinal manifestations, younger age or perianal disease at diagnosis, smoking, endoscopic severity, serologic reactivity to microbial antigens, and certain genetic mutations (e.g., NOD2).[21] These factors may represent a first step in stratifying patients into low or high-risk groups to determine appropriate treatments and therapeutic targets.

Early Use of Biologic Therapy is Associated with Improved Outcomes

Biologic medicines, including adalimumab and vedolizumab, have provided much needed alternatives to steroid-based therapy in patients with CD. Moreover, early use of biological therapies is associated with improved treatment outcomes of clinical remission and mucosal healing. In a real-world observational study of 650 patients, those who received early vedolizumab (≤2 years from diagnosis) were associated with better clinical remission, steroid-free remission, and mucosal healing compared with those who received late vedolizumab (>2 years from diagnosis).[22] Another real-world study of 122 patients demonstrated significantly fewer CD-related flares in patients receiving early vedolizumab compared with those who received late vedolizumab.[23]

The REACT study,[24] an open-label, cluster randomised clinical trial, evaluated the strategy of early intervention with combined immunosuppression (ECI) with adalimumab therapy, versus conventional management. For the ECI strategy, disease activity was assessed every 12 weeks and treatment was modified if necessary. Conventional management was a step-care sequential algorithm according to the usual practice of the physicians. Stating the case for fast decision making, the ECI strategy with regular assessment and intervention resulted in reduced risk of hospitalisation, surgery, or serious disease-related complications versus conventional management.[24]

Although there is a consistent trend towards the increased use of biologics over time, many patients with CD still do not receive them. For example, in 2014, only around one-third of CD patients in Norway had ever received a biologic for treatment of CD.[25] An important contributing factor to the limited use of biologics may be safety concerns. A survey of patients with IBD evaluated the attributes of biologic treatment (i.e., mechanism of action, mode of administration, efficacy, and side effect profile) that drive treatment decision making. Patients with CD were found to prioritise safety attributes over all other attributes, demonstrating the importance of minimising side effects.[26] A comparative safety study in the real-world setting using matched propensity scores has shown vedolizumab to be associated with less serious infections and serious AE compared to TNF antagonist treatment.[27]

Multidisciplinary Care Improves Outcomes

Prof Schreiber also emphasised that early and appropriate therapy should be delivered by a structured and collaborating MDT, putting the patient at the centre to ensure optimal treatment is provided. Patients with early-stage CD are often treated in a community setting,[28] but this should not prevent access to a MDT.

Fistulising Crohn's Disease: Current Treatment Challenges

Professor Gert van Assche

While the other speakers focussed on the beneficial effects of early intervention, Prof van Assche concentrated on a typical late-stage Crohn's complication. Fistulas are one of the most frequent and disabling complications of CD. A population-based cohort study reported that the cumulative incidence of fistulas rises steadily from approximately 20% within the first year of diagnosis to 50% after 20 years, with almost half of these cases having perianal manifestations.[29] A perianal fistula is the initial disease presentation in approximately 10% of patients with CD and may precede the manifestation of intestinal disease by several years.[30] Delays in diagnosis of CD in the presence of fistulas is a significant problem, which may be attributed to late referral of patients to a gastroenterologist or to a centre with IBD expertise.

Perianal fistulas negatively impact on patients' QoL and are often persistent despite treatment.[31,32] The presence of fistulas is known to predict a disabling disease course[33] and half of complex cases require complicated surgical interventions, such as stomas, resection, and proctectomy.[34] Physical symptoms, such as anal pain and discomfort, and restriction of daily and sexual activities, are important concerns for patients.[32,35] Moreover, patients are reluctant to talk about the impact of perianal disease on their daily lives and patient reporting of the burden is influenced by intercultural differences. As such, there is a substantial unmet medical need for improved treatment options.

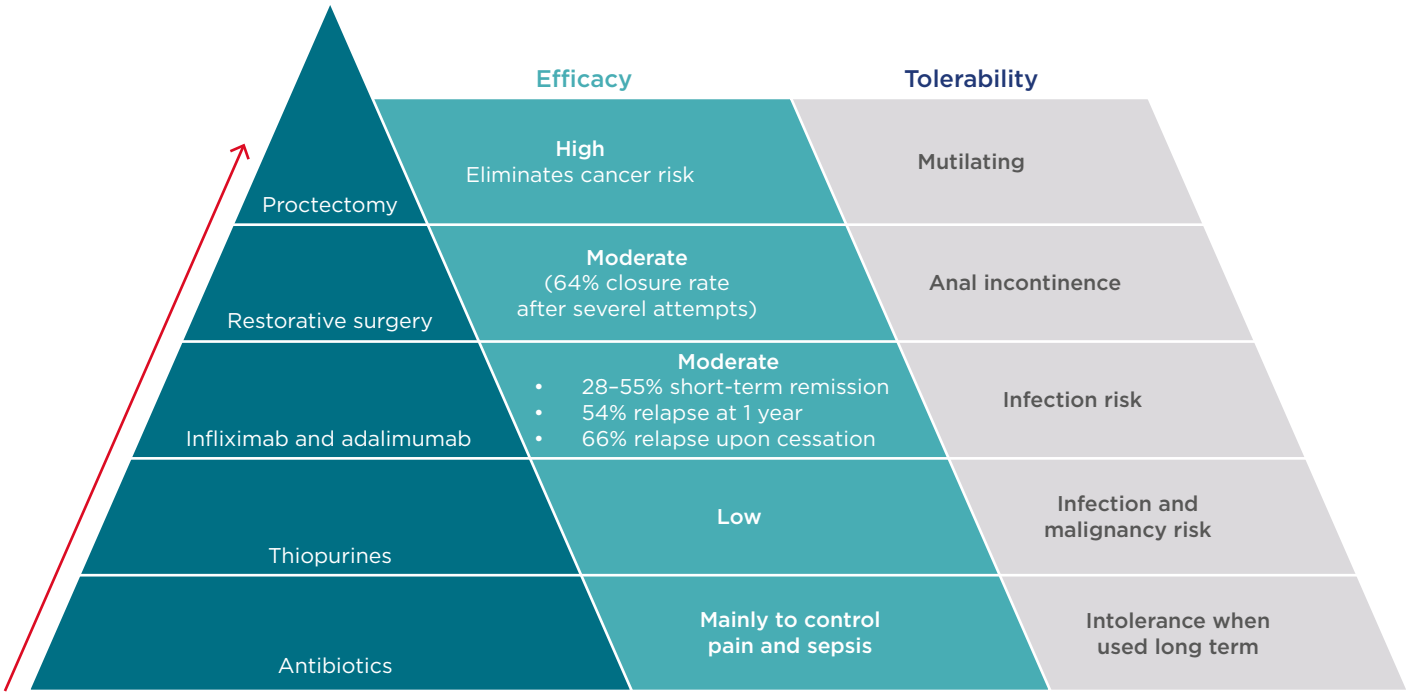

Figure 2: Step up treatment algorithm for perianal Crohn's disease.

The currently accepted treatment algorithm for perianal Crohn's disease is based on the concept of 'step-up' therapy, progressing antibiotics through biologic therapy to surgical techniques.

Perianal Fistulising Crohn's Disease is a Complicated Treatment Challenge

The short-term goals for treatment of perianal fistulas in CD are to drain abscesses and reduce symptoms. In the longer-term, aims are to halt any discharge and ensure healing, improve QoL, preserve continence, and avoid proctectomy.[36] Overall, treatment should be individualised according to the type of fistula, degree of rectal inflammation, and severity of symptoms.[37]

Several treatment options are available, and a 'step-up' algorithm is generally used (Figure 2). After initial treatment with antibiotics and thiopurines, which are useful adjunctive treatments despite their limited and unproven efficacy when used alone, biologic therapies are often used as the next option. Biologics provide effective short-term remission of fistulas in approximately 28–55% of patients.[7,38] However, >50% of these patients are likely to relapse within 1 year[39] or after cessation of therapy.[40] In one study, MRI-based disease activity scores demonstrated that infliximab had a major impact on perianal fistulas in the short and medium-term. Of note, efficacy was not maintained long-term, and at 95 weeks there was no significant difference in MRI score versus baseline.[41]

After exhaustion of drug-based therapeutic options, surgical procedures become necessary but are poorly tolerated. Restorative surgery can be successful for some patients, but the fistula closure rate is only moderate[42] and there is a risk of anal incontinence. Proctectomy is recommended only as a last resort[36] as, although highly effective, it is a mutilating procedure with considerable risks, including pelvic nerve damage, presacral abscesses, and delayed perineal wound healing. Unfortunately, owing to the limitations of other treatment options, proctectomy remains a reality faced by many patients with CD.[36]

By reviewing the evidence of pharmacological therapy in conjunction with surgical treatments, the paucity of effective treatments for patients with fistulising CD is apparent and represents a significant unmet need. A novel and innovative technique using stem cell therapy to treat complex perianal fistulas has received marketing authorisation in Europe. This therapy, darvadstrocel (Alofisel®, Takeda Pharma A/S, Taastrup, Denmark), previously Cx601, is available for patients with non-active/mildly active luminal CD, who have shown an inadequate response to at least one conventional or biologic therapy and looks promising for this hugely underserved population of patients.

Transforming Treatment of Fistulising Crohn's Disease: New Stem-Cell Based Approaches

Professor Damián García-Olmo

Prof García-Olmo further accentuated that patients with fistulising CD are highly challenging to treat and that there is a lack of effective treatments. Patients with fistulising CD are known to be particularly refractory to conventional medical strategies of antibiotics, immunomodulators, and TNF antagonists. Pharmacological therapies serve to provide a degree of symptom improvement often in the short-term, but long-term complete healing is rare. Ultimately, surgical procedures become inevitable after repeated relapses. A number of surgical options are available for the treatment of fistulas, including obturation (fibrin glue and/or fistula plugs), chronic seton placement, endorectal mucosal advancement or local perineal flaps, sphincteroplasty, and ligation on the intersphincteric tract (LIFT).[43,44] However, each of these options is associated with at least one important limitation, such as a medium or high rate of fistula recurrence, anal incontinence, postoperative pain, and/or the technical difficulty of performing the procedure. Therefore, there is a clear need for effective late-stage treatments or procedures that are not associated with any of these issues.

Stem Cell Therapies Offer the Potential for Improved Fistula Healing

The essential conundrum of therapy for perianal fistulas is the difficulty of inducing wound healing. The anti-inflammatory and immunomodulatory properties of mesenchymal stem cells offer the potential to induce healing of the fistula without the need for gastrointestinal tract surgery.[45]

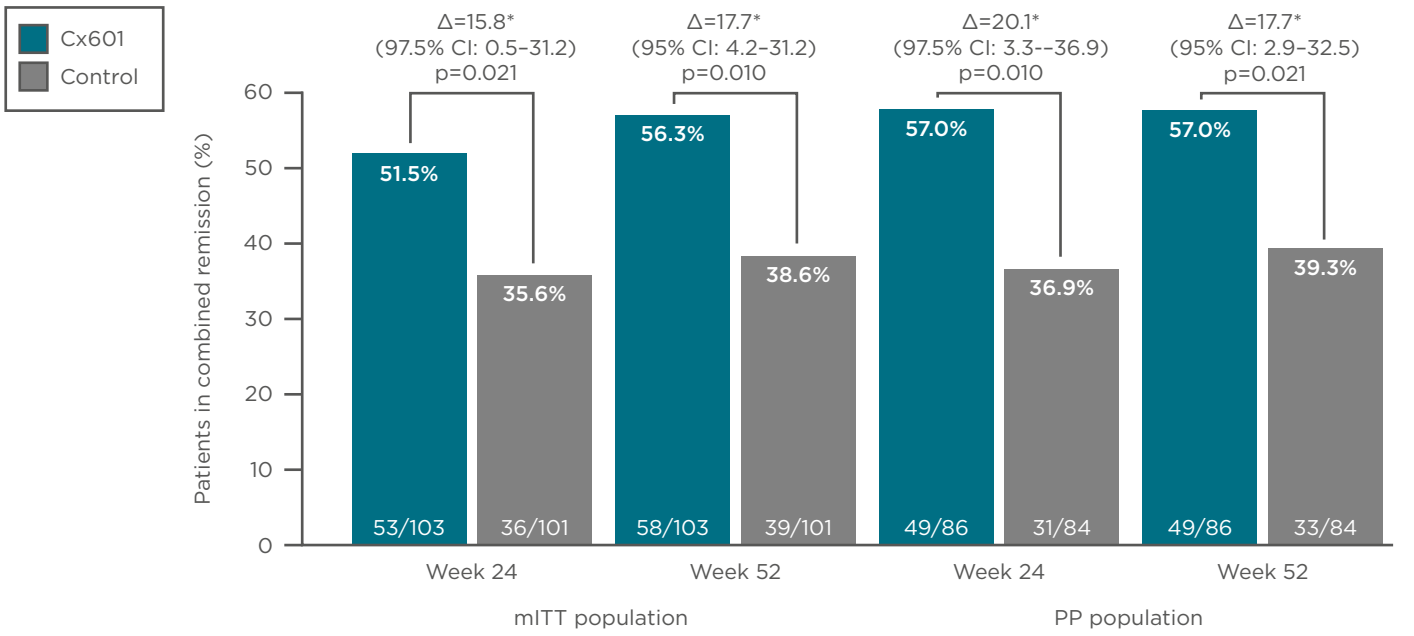

Figure 3: Combined remission of perianal fistulas at Week 24 and Week 52 following treatment with Cx601 or placebo.

CI: Confidence interval; mITT: modified intention to treat; PP: per protocol.

Adapted from Panés et al.[51] and Panés et al.[52]

Clinical proof of concept was first demonstrated in 2003 using autologous adipose-derived stem cells (ASC) for the successful treatment of a young woman with a recurrent rectovaginal CD fistula unresponsive to medical treatment.[46] Further Phase I and II studies presented positive data for autologous ASC for the treatment of complex perianal fistulas in patients with CD, with induction of healing observed in 70–82% of patients and no AE considered to be related to treatment with ASC.[47-49]

In clinical practice, the use of allogeneic stem cells is preferable to autologous stem cells because it avoids the need to collect primary cells from the patient. The feasibility of this option could provide an 'off-the-shelf' treatment that would be accessible to more patients, more affordable, and be available for more rapid administration.[50] In recent years, investigations into the use of stem cell therapy in CD has focussed on the use of allogeneic stem cells with promising results.

Allogeneic Adipose-Derived Stem Cells are a Promising Option for the Treatment of Complex Fistulas

ADMIRE[51] was a Phase III, randomised, double-blind, placebo-controlled trial that assessed the efficacy and safety of allogeneic ASC (darvadstrocel) for treatment-refractory complex perianal fistulas in adult patients with CD. Patients received standard of care plus either darvadstrocel or placebo. The primary endpoint was combined remission at Week 24, defined as the closure of all treated external openings that were drained at baseline (clinical remission) and absence of collections >2 cm of the treated perianal fistulas, confirmed by blinded central MRI.[51]

The proportion of patients who achieved combined remission was significantly higher with darvadstrocel treatment compared with placebo at Week 24 (51.5% versus 35.6%; p=0.021) and was maintained at Week 52 (56.3% versus 38.6%; p=0.010) (Figure 3).[51,52] Median time to clinical remission occurred at around 7 weeks in the darvadstrocel group and 15 weeks in the placebo group, indicating

that darvadstrocel treatment also resulted in more rapid healing than the current standard of care.[53] Relapse rates at Week 52 were lower with darvadstrocel compared with placebo (25.0% versus 44.1% [95% confidence interval: -39.5–1.3]),[53] which is particularly encouraging given that approximately half of patients treated with antiTNF therapy for perianal fistulas experience a recurrence.[54] The safety data at Week 52 confirmed a favourable tolerability profile for darvadstrocel, which was maintained over a prolonged period and the frequency and type of AE was similar in the two groups.[52]

These findings have potentially significant implications for the treatment of perianal fistulas in clinical practice. The sustained response observed with darvadstrocel could reduce the need for major surgical interventions, resulting in lower risk of incontinence, and reduce the need for systemic immunosuppression, providing a more benign tolerability profile. Stem cell therapy is therefore a pivotal step to addressing the unmet need for a safe and effective treatment of complex perianal fistulas in CD.

Concluding Remarks

Current evidence suggests that there may be a 'window of opportunity' for earlier, timely intervention with DMAID to change the natural progression of CD and prevent or reduce future debilitating complications. Evidence from clinical trials suggests that the use of vedolizumab in early-stage disease is associated with better clinical remission and mucosal healing compared with late-stage disease. In later stages of the disease, fistulising CD continues to present a particularly complex clinical challenge, with current treatment options limited by low success rates, tolerability issues, and the risks associated with surgical procedures. Alofisel stem cell therapy is a promising new option for fistulising CD, which addresses many of the pitfalls of current treatment options and is associated with a growing body of clinical evidence demonstrating efficacy and safety. Care for patients with CD should involve a well-aligned MDT to ensure effective management of the diverse burden of disease, supported by clear patient communication, at all stages.

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