

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Corticosteroid-Free Remission in Patients With Inflammatory Bowel Disease



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G&H Currently, when might corticosteroids be used in patients with inflammatory bowel disease?

BS Corticosteroids remain an important element in the treatment of inflammatory bowel disease (IBD). Studies have demonstrated the efficacy of corticosteroids in rapidly controlling inflammatory activity in both ulcerative colitis and Crohn's disease. Even with the development of biologics and small molecules that have different mechanisms of action, at the end of 1 year of treatment in clinical trials, most of these therapies have only achieved a clinical remission rate that varies from approximately 30% to 50%. When patients do not respond to treatment, corticosteroids often end up being used until new medication is initiated. In addition, patients who initially respond well to advanced therapies may lose response during the maintenance phase. At this point, corticosteroids are often restarted until a new therapy proves effective in controlling the disease. Thus, despite the numerous advances in IBD treatment options, particularly in recent years, this class of drugs is still widely used to control symptoms, induce response, or achieve clinical remission.

G&H What are the disadvantages of using corticosteroids, especially long term, in the management of patients with IBD?

BS A good deal of data have shown that corticosteroids are not only ineffective in maintaining long-term remission, but they are also associated with numerous adverse effects and complications, such as weight gain, diabetes,

osteoporosis, osteonecrosis, and increased infection risks. Studies have also shown that corticosteroids are even associated with an increased risk of mortality. Therefore, clinicians often try to decrease the use of corticosteroids, especially long term, in patients with IBD. Data have shown that corticosteroid use has decreased over the years, but there is still a need to create strategies to further reduce such use. The negative effects of corticosteroids have also reinforced the need to explore safer therapeutic alternatives for the maintenance of remission in IBD.

G&H How are corticosteroids typically tapered in clinical practice and trials?

BS Generally, IBD guidelines recommend that corticosteroids should be used for no more than 12 weeks. Therefore, clinical practice protocols advise a gradual reduction of the dose each week over a period of 8 to 12 weeks. Depending on the speed of action of the drug being used, faster tapering can lead to the need to restart corticosteroid treatment or even revert to the previous effective dose.

Regarding tapering in randomized controlled trials, several points deserve discussion. The first involves when tapering starts. Most studies begin corticosteroid tapering after the induction phase, which generally occurs from the sixth to twelfth week. However, in the U-EXCEL/U-EXCEED studies on upadacitinib (Rinvoq, AbbVie), for example, tapering occurred earlier, in the fourth week, still within the induction phase. Another point is whether tapering was mandatory (ie, forced). For example, forced tapering was seen in the PURSUIT-Maintenance study, which evaluated the efficacy and safety of golimumab

(Simponi, Janssen) in ulcerative colitis; the True North study, which assessed the efficacy and safety of ozanimod (Zeposia, Bristol Myers Squibb) in ulcerative colitis; and the U-EXCEL/U-EXCEED/U-ENDURE studies, which examined the efficacy and safety of upadacitinib in Crohn's disease. This is an important issue, as these studies were more rigorous by not allowing the use of corticosteroids during the maintenance phase, emphasizing the corticosteroid-sparing nature of the drug being studied.

G&H How well can corticosteroid-free remission be achieved with the current IBD therapies, especially the newer ones?

BS Over the past 25 years, corticosteroid-free remission has been an endpoint assessed in most randomized controlled trials of advanced therapies in IBD, such as biologics and small molecules. Since the initial studies, it has been observed that corticosteroid-free remission was achieved more significantly with biologic therapies than with the placebo group. For example, in the ACT 1 study, which was published in 2005 and assessed the efficacy and safety of infliximab in moderate to severe ulcerative colitis, biologic therapy was more effective in inducing clinical remission with corticosteroid discontinuation than placebo. Drugs more recently approved by the US Food and Drug Administration for the treatment of ulcerative colitis and Crohn's disease have also demonstrated efficacy in achieving corticosteroid-free remission. For example, in the ELEVATE study, which evaluated the efficacy and safety of etrasimod (Velsipity, Pfizer) in patients with moderate to severe ulcerative colitis, etrasimod promoted corticosteroid-free remission after 52 weeks of treatment in 32% of patients, compared with just 7% in the placebo group. Corticosteroid-free remission was also evaluated as an endpoint in the U-ENDURE study, which assessed the efficacy and safety of upadacitinib in Crohn's disease. In this randomized controlled trial, the Janus kinase (JAK) inhibitor was able to promote corticosteroid-free remission in 40% of patients compared with just 4.5% in the placebo group. These data show that there are many options for achieving corticosteroid-free remission at the present time.

G&H What factors increase the difficulty of achieving and maintaining corticosteroid-free remission in patients with IBD?

BS In some cases, corticosteroid-free remission is quite difficult to achieve and maintain. As previously mentioned, a good deal of data have shown that more than half of patients will not respond to the advanced IBD therapies currently available. Just like other therapeutic

targets, attaining and maintaining corticosteroid-free remission can be more challenging in certain IBD patient groups. Factors such as longer disease duration, more extensive disease, more aggressive phenotypes, smoking, and previous biologic therapy use are often linked to greater difficulty with treatment response. For example, in the UNIFI study, which evaluated the efficacy and safety of ustekinumab (Stelara, Janssen) through 3 years of maintenance therapy, the rate of corticosteroid-free symptomatic remission was greater for biologic-naïve patients than patients with a history of biologic failure. Similarly, in a post hoc analysis of GEMINI 1, investigators concluded that factors such as no previous anti-tumor necrosis factor exposure or short disease duration were associated with sustained corticosteroid-free remission in patients with ulcerative colitis who received vedolizumab (Entyvio, Takeda). Studies have also shown that patients who achieve endoscopic remission may experience a longer period without flares and higher rates of corticosteroid-free remission.

Additionally, several ongoing studies are assessing whether genetic factors, composition of the intestinal microbiota, and pharmacokinetic properties of the drugs used in advanced therapies are associated with more predictable response to treatment, including corticosteroid-free remission.

G&H Have studies demonstrated that corticosteroid-free remission is associated with outcomes such as mucosal healing and decreased risk of disease progression?

BS Corticosteroid-free remission occurs more frequently in patients with mucosal healing. These two endpoints are closely linked. Studies have shown that patients who achieve endoscopic remission have a greater chance of not requiring long-term corticosteroid use.

Corticosteroid-free remission has often been used as a secondary endpoint in clinical trials, but its direct impact on reducing disease progression remains under-researched in the medical literature. However, because corticosteroid-free remission is associated with other important objective outcomes, such as mucosal healing, it may also be seen more often in patients who experience less progression of their disease over time.

G&H Should corticosteroid-free remission still be included as an endpoint in clinical trials when there are other therapeutic targets?

BS Even in the pre-biologic therapy era, corticosteroid use was a rather significant concern; therefore, randomized controlled trials have adopted corticosteroid-free

remission as one of the endpoints studied over time. This has continued in studies conducted more recently. Corticosteroid-free remission is considered to be highly relevant because when overall clinical remission is analyzed as an endpoint, some patients may be doing well only with the help of systemic corticosteroid therapy, even at the end of the maintenance phase of a randomized controlled trial. When comparing the rates of overall clinical remission with corticosteroid-free remission in a recent systematic review, investigators concluded that clinical remission can be approximately 20% to 25% higher than corticosteroid-free remission, perhaps because many patients achieve clinical remission under the influence of a corticosteroid therapy. I believe that corticosteroid-free remission should be part of endpoints not only for randomized controlled trials but also for real-world studies.

G&H What is the place of corticosteroid-free remission in the ultimate goal for IBD treatment?

BS Controlling symptoms and feeling better are important goals shared by patients and doctors. However, in IBD there is also a need to focus on long-term targets that are important. Corticosteroid-free remission goes beyond controlling symptoms. It is the maintenance of a state of total or near absence of symptoms without the need for corticosteroids. It is not just being well, but being well without needing corticosteroids. This outcome is also significant because it adds safety by eliminating the risks associated with long-term corticosteroid use. Once this is achieved, physicians face other challenges such as reaching additional therapeutic targets like endoscopic remission, which is currently considered a cornerstone in the treatment of IBD. Endoscopic remission is associated with significant reduction in the progression of intestinal damage and therefore a lower risk of IBD-related complications such as hospitalizations, surgeries, and cancer. Thus, corticosteroid-free remission is also important because it is associated with these deeper targets that need to be achieved.

G&H What further research is needed regarding corticosteroid-free remission?

BS It is necessary to develop and standardize better protocols in clinical studies to promote the rational use of corticosteroids in the induction and maintenance phases. More transparent protocols for corticosteroid usage and tapering would enable better analysis of the true corticosteroid-sparing power of the medications being tested. Additionally, it is important to study potential strategies that could further minimize corticosteroid use in clinical

practice, especially because of the emergence of new therapeutic options with rapid onsets of action and proven efficacies in inducing and maintaining clinical remission, such as JAK inhibitors. For instance, recent evidence regarding the role of JAK inhibitors in severe acute colitis suggests that these medications could avoid the need for intravenous corticosteroid therapy. Further research is needed.

G&H Are there any other needs in the community?

BS Better education is needed for patients and general practitioners regarding the risks of long-term corticosteroid use. Effective patient education is essential for managing chronic conditions. It is crucial for patients to understand their condition, the treatment options, and the risks associated with corticosteroids. This knowledge can encourage informed decision-making and adherence to treatment plans. Well-informed patients are more capable of communicating side effects to their doctors for timely treatment adjustments. Understanding corticosteroid risks can motivate adherence to alternative therapies and lifestyle changes, reducing long-term dependence and potential side effects. Overall, comprehensive education about corticosteroids improves the doctor-patient relationship, encouraging a collaborative approach to health care that is essential for achieving optimal health outcomes.

Disclosures

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Suggested Reading

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