Biodrugs 2010; 24 Suppl. 1: 1-2
1173-8804/10/0001-0001/$49.95/0

The current goal of medical management of Crohn's disease (CD) is to induce and maintain remission and improve the patient's quality of life. The choice of drug therapy is guided by severity as well as by disease course over time. Although corticosteroids are associated with high initial rates of response, a considerable proportion of patients either fail to respond or become steroid-dependent. Corticosteroids do not maintain remission, prevent recurrence of disease after resection or heal the mucosa. Under the 'step-up' treatment paradigm, the probability of surgery remains high and a significant proportion of patients will also suffer intolerable side effects. Recent studies have shown that the use of systemic corticosteroids is associated with adverse outcomes such as serious infections and increased mortality. Although methotrexate and the purine antimetabolites, 6-mercaptopurine (6-MP) and azathioprine (AZA), have shown to be of significant benefit in steroid-dependent patients and in maintaining remission, their long-term benefit in altering the natural history of the disease remains debatable.

The use of scheduled infliximab (IFX) infusions has been shown to be superior to episodic infusion regimens in terms of maintaining remission and reducing the risk of developing immunogenicity. In addition, in non naive patients, the use of concomitant immunosuppressant therapy with scheduled maintenance doses does not appear to confer any benefit.[1] Furthermore, sustained mucosal healing associated with infliximab therapy may lead to reduced rates of hospitalization and may translate to an altering of the natural progression of CD. Earlier treatment may have a disease-modifying effect and has proved to be useful. Results from the recent SONIC (Study Of biologic and Immunomodulator Naive patients In Chrohn's disease) study, in which infliximab treatment with or without azathioprine was compared in CD patients naive to both immunosuppressants and biologic therapy, shed some light on the established CD paradigm.[1] The clinical background of the SONIC population included: 1) steroid-dependency or the requirement of a second (or greater) round of corticosteroids within 1 year; 2) 5-aminosalicylic acids (5-ASA) failures; 3) budesonide failures; 4) presenting moderate or severe CD activity. At 26 and 50 weeks of treatment, infliximab was superior in comparison to azathioprine regarding corticosteroid-free remission. In patients with elevated baseline C-reactive protein (CRP) and mucosal lesions, infliximab monotherapy or combination therapy (IFX + AZA) proved to be twice as effective as azathioprine monotherapy. Moreover, the proportion of patients with complete mucosal healing at week 26 in the combined treatment group was twice that of the monotherapy azathioprine group. The results of this landmark trial could serve as a premise for clinicians to question existing therapeutic strategies. First, anti-tumor necrosis factor (TNF) treatments have been shown to be superior to azathioprine in immunomodulator-naive CD patients. Second, CRP levels and endoscopy are essential predictors of a better response to infliximab. Third, in patients with normal baseline CRP and endoscopy, with clinical activity, alternative explanations for symptoms should be sought before therapeutic escalation. Fourth, infliximab is currently the most effective drug in mucosal healing. Finally, patient selection is indisputably crucial for a 'top-down' strategy due to some concerns relating to the risk of lymphomas with combined treatment (AZA + IFX).

We are currently experiencing new and challenging concepts in the treatment of CD. Perhaps fully advocating a top-down approach may be premature, however earlier treatment with biologics may have a disease-modifying effect and ultimately alter the course of CD. The future will be dictated by the advent of new targets and the pursuit of mucosal healing as a therapeutic goal, although prospective studies are needed in this matter.

In this supplement to *BioDrugs*, several challenging cases of inflammatory bowel disease (IBD) are published. It is evident that new drugs, namely biologics, were an effective option in the treatment of these patients. In cases of severe ulcerative colitis refractory to corticosteroids, penetrating CD, IBD with difficult extraintestinal manifestation, and severe cases of luminal CD, biologics transformed the medically refractory into the medically treatable. Moreover, they improved the patients' quality of life and decreased the number of hospitalizations and surgeries. In the past ten years medical options for IBD have improved and it is now possible to offer patients a quality of life comparable to the general population. Nevertheless, it is important to emphasize that the cornerstone of the correct current management of IBD is based on recognizing patients with severe disease. Early identification of patients with poor prognoses, effective treatment, and new therapeutic targets such as mucosal healing signify new frontiers in the management of IBD patients.

Fernando Magro

Portuguese Group of Studies of Inflammatory Bowel Diseases;
Gastroenterology Department of Hospital de São João;
Institute of Pharmacology and Therapeutics – Faculty of Medicine,
Oporto University, Portugal

Reference

1. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010; 362 (15): 1383-95