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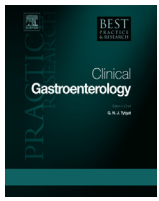

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Can we get more from our current treatments?

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A B S T R A C T

Crohn's disease is a chronic incurable condition that normally requires lifelong treatment. Whilst the anti-TNF agents have revolutionised the management of Crohn's disease over the last fifteen years, they are not a panacea. In particular, in part due to their immunogenic nature, loss of response limits their long term effectiveness in many patients. The only other long term disease-modifying options are the immunomodulators, methotrexate, azathioprine and mercaptopurine. Therefore, given the limited number of drugs available to treat Crohn's disease, it is important that efforts are made to ensure that drugs are used in the best way possible as once a drug is deemed ineffective, it is rarely used again. For the growing number of patients who have active disease despite having been exposed to all standard therapies, failure to optimise drug therapy may lead to missed opportunities in the management of their disease. In this review, optimisation of drugs commonly used in the management of Crohn's disease will be discussed.

Introduction

Crohn's disease is a chronic incurable condition, the aetiopathogenesis of which is only partially understood. However, over the last two decades our understanding of the fact that, at least for some

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patients, it is a progressive, destructive disease has led to a change in treatment paradigms. Accordingly, more attention has been paid to adopting treatment strategies that may alter the natural history of Crohn's disease with greater focus being placed on harder outcomes, such as mucosal healing, in an attempt to prevent hospital admission, the need for surgery and, ultimately, disease-associated disability. Anti-TNF therapy, which has proved to be the most effective long term therapy available for Crohn's disease, has been available for over a decade and has revolutionised the management of moderate and severe Crohn's disease. However, it is not a panacea; whilst response and remission rates in 'real-life' practice are markedly higher than those seen in clinical trials, not all patients respond to treatment with these agents. Furthermore, largely due to immunogenicity, secondary loss of response rates are somewhere in the region of 10–15% per year. Finally, anti-TNF agents are expensive, accounting for a significant proportion of healthcare costs of patients with Crohn's disease.

Thus, the armamentarium of drugs available for the treatment of Crohn's disease remains limited, recognised maintenance treatments in most of the world being limited to thiopurines, methotrexate and the two widely available anti-TNF agents (adalimimuab (ADA) and infliximab (IFX)). It is for this reason, in contrast to parallel specialties such as rheumatology where the range of available disease-modifying drugs is broader, that significant emphasis has been placed on maximising the response to individual therapies in Crohn's disease. In this review, methods of optimising treatment will be addressed, focussing on the individual drugs used to treat Crohn's disease as well as on treatment strategies which may improve outcome.

Corticosteroids

Corticosteroids should be given at standard doses (40–60 mg or 0.75–1 mg/kg of prednisolone or equivalent; 9 mg budesonide) as a decreasing course. An exit strategy should be planned when starting steroids as they should only be used as induction agents. This will often include the initiation of a steroid-sparing agent.

Corticosteroids are highly effective agents at inducing symptomatic remission in patients with Crohn's disease but have no place in maintaining remission [1]. Unfortunately, their ability to improve symptoms in the majority of patients is only reflected by mucosal healing in the minority, the highest reported rates being up to 29% in patients who achieve clinical remission [2]. Furthermore, their side effect profile makes treatment beyond induction unacceptable. Thus getting more from treatment with corticosteroids relates to using the correct dose to induce remission, to the avoidance of side effects, and to avoiding inappropriate use.

When considering induction of remission, there is a lack of high quality evidence regarding what dose should be used. Whilst clearly there is a dose response up to a point, the ceiling is less clear. Doses in the region of 40–60 mg or 0.75–1 mg/kg of prednisolone (or equivalent) induce remission in up to 83% of patients [3]. Dose reduction thereafter, rather than sudden withdrawal, is normal practice although high quality evidence supporting this is limited. Indeed, the only randomised trial addressing dose reduction, compared two different withdrawal regimens, a rapid withdrawal over four weeks and a slower withdrawal over 12 weeks; no difference was found in the relapse rate at six months [4].

Thus, when it comes to getting the most out of steroids, greatest attention has appropriately been paid to minimising toxicity rather than to maximising efficacy. This can be thought of in two ways; first, avoiding inappropriate use, and second using preparations that decrease toxicity without sacrificing efficacy. The former is best achieved by always considering a withdrawal strategy when initiating steroids. Given that long term steroid-induced remission is relatively rare in Crohn's disease, occurring in 44–56% of cases one year after the initiation of a single course of steroids [1], it is normal practice to consider starting a steroid-sparing agent to maximise the chance of maintaining remission after steroids are withdrawn.

Budesonide undergoes high first pass metabolism and is also poorly absorbed from the gastrointestinal tract. Thus, whilst less effective than prednisolone (relative risk 0.86, 95% CI 0.76–0.98), it remains an appropriate treatment for people with ileocaecal Crohn's disease in view of its superior safety profile. [5] The superior efficacy of prednisolone is particularly marked in patients with severe disease such that budesonide is probably best used in patients with moderate disease.