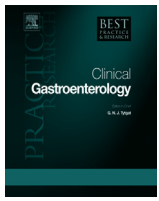
Best Practice & Research Clinical Gastroenterology 28 (2014) 473–483

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology



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Treatment algorithms in Crohn's – Up, down or something else?

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Keywords:
Crohn's disease
Anti-TNF
Step-up
Top–down
Mucosal healing

A B S T R A C T

Crohn's disease is a chronic, progressive and disabling condition. New therapeutic goals have emerged in Crohn's disease such as the need to look beyond symptoms by achieving mucosal healing that is known to be associated with better outcomes. Anti-TNF (Tumour Necrosis Factor) therapy is the most potent drug class to induce and maintain mucosal healing in Crohn's disease. Recent evidence indicates that the efficacy profile of thiopurines has been overestimated while the increased risk of malignancies (lymphoma, non-melanoma skin cancers, myeloid disorders) has been underestimated. Methotrexate is well-tolerated, but its potential for disease modification is unknown. Achieving mucosal healing in patients with early Crohn's disease might be the best way to change disease course and patients' life. In 2014, anti-TNF treatment should be the first-line therapy in patients with Crohn's disease who suffer from severe and/or complicated disease and in those with poor prognostic factors. In the remaining patients, a rapid step-up approach based on a tight monitoring is recommended.

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http://dx.doi.org/10.1016/j.bpg.2014.05.001
1521-6918/

Introduction

Crohn's disease (CD) is a chronic progressive and disabling condition. Anti-TNF (Tumour Necrosis Factor) therapy has changed the way of treating inflammatory bowel disease (IBD) refractory to standard medications. Anti-TNF therapy is associated with fewer surgical procedures, fewer hospitalizations, better quality of life, steroid sparing, greater clinical remission and mucosal healing rates in both CD and ulcerative colitis [1–7]. A growing body of evidence indicates that we need to look beyond symptoms by inducing and maintaining mucosal healing [8,9]. Mucosal healing is associated with fewer surgical procedures, fewer hospitalizations, better quality of life and steroid tapering [10]. As anti-TNF therapy is the most potent drug class in IBD, some proponents of a top–down approach argue that starting with drugs such as thiopurines for which the potential for disease modification is debated is a missed opportunity to change disease course and patients' life. However, the increasing use of biologics has raised some safety concerns and the cost-efficacy of strategies based on a wider and earlier use of biologics has yet to be determined.

Herein, we review the advantages and drawbacks of step-up vs. top–down strategies for IBD before giving some recommendations for clinical practice.

Step-up approaches: pros and cons

Current therapeutic strategies did not dramatically change the natural history of CD [11].

In the pre-biologics era, in a population-based cohort from Olmsted County [12], the five-year cumulative probability of first major abdominal surgery ranged from 35.1% (95% confidence interval (CI), 22.8–45.9%) in patients diagnosed in 2000–2004, to 43.7% (24.3–58.8%) in those diagnosed between 1980 and 1984, major abdominal surgery rates remained stable, with five-year cumulative probabilities in 1970–1974 and 2000–2004 of 37.5 and 35.1%, respectively. A separate proportional hazards model using the total cohort ($n = 310$) to assess the association with calendar period (using the period 1970–1974 as a reference) indicated the cumulative risk of a first major abdominal surgery remained stable over the past four decades ($p = 0.60$) [12].

In the biologics era the need for surgery remains high in CD. In the Nancy IBD cohort [13], including 296 patients newly diagnosed with CD, 76 (26%; 95% CI, 21%–31%) underwent at least one major abdominal surgical procedure after a median follow-up of 57 months [13].

Several studies [13–15] found that thiopurine use was associated with reduced need for surgery in CD. However, these retrospective studies are only association studies and no conclusions can be drawn from these cohorts on the potential for disease modification of thiopurines. Thiopurines have shown some benefit in maintaining remission and steroid sparing in some small controlled trials [16–18].

A recent meta-analysis [19] showed that azathioprine and six-mercaptopurine may allow patients to reduce steroid consumption, but azathioprine therapy is inferior to infliximab for induction of steroid-free remission.

Recently, two controlled trials, namely AZTEC and RAPID, demonstrated that early introduction of azathioprine in the course of CD, was not more effective than 'conventional' management; after 76 weeks of treatment, 30 patients treated with azathioprine (44.1%) and 23 given placebo (36.5%) were in sustained corticosteroid-free remission (difference of 7.6%; $p = 0.48$) in the AZTEC trial [20]; and the rate of trimesters in remission per patient was 67% in the early azathioprine group and 56% in the conventional management group ($p = 0.69$) in the RAPID trial [21]. However, patient selection and the definition of the primary end-point should be taken into account when interpreting these findings. Indeed, some patients possibly had inactive and/or benign disease at study inclusion while it is now recommended to include patients with objective signs of inflammation such as elevated fecal calprotectin level, elevated CRP level and/or the presence of mucosal ulcerations. Furthermore, objective outcome measures such as mucosal healing should be considered in CD trials and not only clinical symptoms that are highly subjective. It makes the potential for disease modification of azathioprine questionable in CD [22].

Furthermore, thiopurines increase risk of malignancies. In a nationwide prospective observational cohort of 19486 IBD patients, called CESAME (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France), which was designed mainly to assess the possible excess risk of