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Drug resistance in inflammatory bowel diseases

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The management of patients with moderate to severe inflammatory bowel diseases, that is, Crohn's disease and ulcerative colitis, remains challenging. In recent years, therapeutic goal evolved from clinical remission to mucosal healing and deep remission. In order to achieve remission, it is important to appropriately choose and use available drugs. Therefore, anti-TNFα treatment should be rapidly used for severe and at-risk patients, sometimes in association with thiopurines or methotrexate. The monitoring of through levels and antibodies to anti-TNFα is relevant to optimize the treatment and to reduce drug inefficacy. However, the development of new drugs is required to offer alternative tools to severe and refractory patients.

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Introduction

Crohn disease (CD) and ulcerative colitis (UC) are two chronic disabling and progressive inflammatory bowel diseases. Their treatment is based on standard medication, immunosuppressive drugs and anti-TNFα therapies. During the last two decades, the strategies used to manage these patients were called step-up and top-down; anti-TNFα treatment, which is the most effective drugs in IBD, is used during the follow-up (step-up) or at the diagnosis (top-down). The dilemma of these approaches is in the one hand to effectively treat severe patients, but in the other hand to not over-treat mild-to-moderate patients. In order to choose an appropriate therapy, it is required to assess the severity of CD or UC with clinical and endoscopic scores. It is also important to follow the efficacy of the treatment with the evolution of these clinical scores and the inflammatory markers, C-reactive protein (CRP) and fecal calprotectin. Moreover, the main goal of the treatment seems to achieve a mucosal healing [1••].

Drug resistance definition

It can be defined as the reduction of drug effectiveness to cure IBD. We will discuss the mechanisms of resistance of corticosteroids, azathioprine (AZA) and 6-mercaptopurine (6-MP), and anti-TNFα, but also the effectiveness of the drugs used in IBD.

In 2015, drug efficacy should be a deep remission, which means mucosal healing and improvement of inflammatory markers, in order to change the course of the disease. Indeed, half of the patients with CD in clinical remission have endoscopic and/or CRP evidence of residual activity in the SONIC trial [2]. In this trial, 20.2% of the patients achieved clinical remission plus mucosal healing plus CRP normalization [3].

Corticosteroid resistance

Conventional therapy of IBD has included corticosteroids, which inhibit T cell activation and pro-inflammatory cytokines [4]. However, 50% of CD and 20% of UC patients fail to respond to glucocorticoid treatment [5]. Several mechanisms of glucocorticoid resistance have been identified: activation of mitogen-activated protein kinase pathways, excessive activation of transcription factor activator protein 1, reduced histone deacetylase-2 expression, raised macrophage migration inhibitory factor, and increased P-glycoprotein-mediated drug efflux [6].

Thus, we believe that corticosteroid should be used at diagnosis in mild or moderate CD patients, in association during 2–3 months with thiopurine analogues, which will be effective to maintain remission by that time. However, in CD children, exclusive enteral nutrition (EEN) is an excellent alternative to corticosteroid and EEN should be proposed alone or in association with thiopurine analogues.

Azathioprine and 6-mercaptourine management

Thiopurine analogues, AZA and 6-MP, are used as a maintenance therapy in IBD. These pro-drugs are transformed into active metabolites, 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPR) [7]. The key enzyme of individual variations in

this metabolism is the thiopurine methyltransferase (TPMT). In the general population, three sub-groups of persons can be separated according to their level of TPMT activity: normal to high (89%), intermediate (11%), and low to absent activity (<1%) [7,8]. A low to absent TPMT activity is associated to an increased 6-TGN concentration and to an increased risk of bone marrow suppression while a very high TPMT activity, which is present in 10% of IBD patients is associated to thiopurine hepatotoxicity and pharmacoresistance [8]. Response to thiopurine analogues appears optimized at 6-TGN levels > 235–250 pmol/8×10^8 erythrocytes [7,8]. A prospective study included 55 IBD patients with steroid-dependency or active disease despite 6 months of AZA treatment; all of them had a normal TPMT activity [8]. AZA dose were increased and metabolites levels were recorded. The authors found that a 6-TGN level > 400 pmol/8×10^8 erythrocytes may predict AZA resistance, with a 100% predictive value. Steroid-free remission was achieved in 43.6% of these patients. Recently, a same level of 6-TGN (405 pmol/8×10^8 erythrocytes) was also predictor of AZA resistance in pediatric IBD patients [9•]. Dose escalation should be stopped when this 6-TGN level is reached, because of drug resistance and increased adverse events.

In CD, thiopurine analogues seem more effective in children [10] than in adults [11]. An early administration of AZA within 6 months after CD diagnosis did not improve its efficacy compared to AZA use in cases of corticosteroid dependency, chronic active disease with frequent flares, poor response to corticosteroids, or development of severe perianal disease [12•].

Physicians should be aware of the increase of malignancies in IBD patients treated by thiopurine analogues, that is, lymphoproliferative disorders and non-melanoma skin cancer [13].

Methotrexate

In IBD, methotrexate is used when patients fail to respond or are intolerant to thiopurine analogues. In a retrospective study, 60–78% of CD and UC patients had a clinical response (steroid withdrawal, CRP normalization or clinical improvement) at 6 months on methotrexate [14]. Nowadays, in a single-centre prospective study of CD patients in clinical remission within at least 3 months, mucosal healing was achieved in only 2/18 (11%) with methotrexate, in 9/18 (50%) with AZA, and in 9/15 (60%) with infliximab [15].

Anti-TNFα treatment

These drugs are used at the onset of the disease in moderate to severe patients or in refractory patients. The results of ACCENT I study have shown that CD patients with a CDAI ≥ 220 who responded to the initial dose of infliximab 5 mg/kg (58%) were more likely to be in remission at week 30 (around 40%) and week 54, to discontinue corticosteroids, and to maintain their response, with repeated infusions at weeks 2, 6 and every 8 weeks [16].

In the CHARM trial, 499/854 CD patients (58%) responded to adalimumab induction, that is, clinical remission (CDAI decrease ≥ 70) [17]. Around 40% of them remained in remission at week 56, either in the adalimumab 40 mg eow (36%) or 40 mg weekly (41%) [17]. In the EXTEND trial, the authors found a 19% rate of deep remission, defined by the absence of mucosal ulceration plus clinical remission (CDAI < 150), in the adalimumab 40 mg group versus 0% in the placebo group at week 52 [18]. To note, this rate of deep remission was greatest when adalimumab was used in patients who had CD for less than 2 years (33%) [18].

In the PRECISE 2 trial, 64% of patients with moderate-to-severe CD had a clinical response after induction with 400 mg certolizumab pegol injections at weeks 0, 2, and 4 [19••]. When this dose was continued every 4 weeks, initial responders were more likely to be in clinical remission at week 26, compared to placebo, 48% versus 29% respectively [19••].

As shown in a randomized controlled trial, infliximab was as effective than ciclosporin in patients with acute severe UC [20]. Treatment failure occurred in 31 (54%) and in 35 (60%) patients respectively given infliximab and ciclosporin respectively.

Some patients generate antibodies to these drugs. Thus, 53/90 (59%) patients developed antibodies to infliximab (ATI) [21•]. ATI were transient in 15/53 (28%) patients. The risk to discontinue infliximab treatment was greater in patients with sustained versus transient ATI (relative risk 5.1) [21•]. Ungar *et al.* found that 42% of CD and UC patients remained ATI-free by 4 years of treatment [22••]. ATI were generally developed within the first 12 months. This incidence was reduced by combined immunosuppressive treatment. ATI development often preceded clinical flare.

A combination of infliximab and AZA was more effective than conventional treatment with corticosteroids ± AZA for induction of remission and reduction of corticosteroid use in newly diagnosed CD patients who had not previously received corticosteroids, antimetabolites, or biological agents [23]. At week 26, 60% patients of the combined immunosuppression group were in remission (CDAI < 150) without corticosteroid and without surgical resection, versus 35.9% in the conventional group ($p = 0.0062$); this difference remained significant at week 52, 61.5% versus 42.2% ($p = 0.0278$). In the SONIC trial, a randomized, double-blind trial, combination therapy with infliximab and AZA was more effective to achieve corticosteroid free clinical remission in moderate-to-severe