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Novel therapeutic targets for inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and Ulcerative Colitis (UC), are immune mediated conditions associated with progressive damage of the inflamed gut tissue, and have a considerable impact on the patient's quality of life. The pathogenesis remains uncertain, but it is clear that complex mechanisms associated with host and luminal factors are involved, generating an unbalance between pro- and anti-inflammatory signaling. It is well established that the purpose of an adequate and complete control of the intestinal inflammation measured not only by clinical symptoms, but also with more objective data such as fecal biomarkers (calprotectin) and endoscopy. The treat to target approach possibly correlates with minor risk for complications associated with IBD, specially surgery and cancer.

The most studied inflammatory pathway in IBD, is described to be dependent of the pro-inflammatory cytokine tumor necrosis factor-alfa (TNF-α), and compose the first line studies for development of biological drugs, in this case, targeting specifically the action of TNF-α. Even though, the use of anti-TNFs drugs are associated with improvement of the inflammation in some patients, a great portion do not respond at first or lose response over time. These findings made clear about the possibility of other mechanisms involved in perpetuating the chronic inflammatory state.

Many years of intensive research have led to the identification of different inflammatory pathways that form the basis of the intensive drug development that we are experiencing today. These novel drugs include agents that target leukocyte trafficking, Interleukin (IL) 23, Janus kinases (JAK), Sphingosine 1 phosphate (S1P) and Smad7, an inhibitor of the immunosuppressive cytokine transforming growth factor β1 (TGF-β1). In this manuscript, we aim to review the most promising late-stage drug candidates for the treatment of IBD.

Contents

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1. Introduction

Crohn's Disease (CD) and Ulcerative Colitis (UC), commonly known as inflammatory bowel disease (IBD) are chronic, progressive and disabling conditions with impaired quality of life, that require lifelong medical treatment and carry out great impact on health and on treatment related costs [1–4].

Complex mechanisms related to the host, such as genetic and innate-adaptive immune system unbalance, together with the interaction with external factors, such as environmental and luminal (i.e., microbial flora), may underlie the pathogenesis of IBD resulting in a disequilibrium between anti- and pro-inflammatory cytokines, leading to a chronic hyper-responsive state [5–7].

The treat-to-target approach, in achieving control of the inflamed gastrointestinal tissue in IBD, including clinical, laboratorial, endoscopic and histologic remission for a prolonged period (deep sustained remission), plays a salutary roll on its evolution and possibly altering the natural history of the disease [8–11]. Hence, emerging therapeutic drugs have become a key step in the management of patients with IBD.

Tumor necrosis factor (TNF)–alfa is a dominant pro-inflammatory cytokine and play a central role in the pathogenesis of IBD [12]. Studies showed that blockage of this inflammatory pathway is associated with effective control of the disease [13,14]. Positive outcomes related to this concept have led to the development of several anti-TNF monoclonal antibodies, infliximab, adalimumab, certolizumab pegol and golimumab, already incorporated into current algorithms on management of IBD [15–21].

Although the introduction of these agents has been a breakthrough in the management of IBD, approximately one third of the patients does not improve after induction therapy (primary non-response). Moreover, loss of response may occur over time (secondary non-response) at considerable rates, in up to 20% per year [22–25]. Hence, new drugs with other mechanisms of action that act on different inflammatory pathways involved in the pathogenesis of IBD are still highly needed [22–25].

Both immune and non-immune components participate in the pathogenesis of IBD. Although TNF-dependent is described to be one of the dominant inflammatory pathways in IBD, other cytokines are observed to be overexpressed in this population. Human and animals models, demonstrate a deregulation on macrophage-induced immune responses to the intestinal microbiota, which leads to a loss of immune tolerance and exacerbation of pro-inflammatory cytokines, with prominence of IL-12 and IL-23. In addition, inhibition of leukocyte trafficking to the gut mucosa has been a second important target for the development of IBD drugs. Blocking anti-bodies inhibit the interaction between leukocytes and the intestinal vasculature, thus decreasing the influx of inflammatory cells into affected gastrointestinal tissues [5–7].

The field of IBD is experiencing an unprecedented period of intensive drug development (Table 1) and it is expected that therapeutic options will increase over the next few years, since many promising clinical trials are ongoing (Table 2). This review will focus on the most promising late stage drug candidates for the treatment of IBD (Fig. 1).

2. Anti-cytokine therapies

2.1. The IL-23/IL-17 pathway

T helper (Th) cells differentiate into T helper cell types Th1 and Th2, producing different sets of cytokines, intrinsic of each pathway. In this scenario, conceptually, CD is characterized as a Th1 cytokine-mediated disease. IL-12 is a heterodimeric cytokine composed of a p40 and a p35 subunit, and have the capacity to promote a Th-1-like immune response, implicated in the pathogenesis of CD. In fact, it has been demonstrated that CD patients, exhibit increased production of IL-12 in the lamina propria, compared to placebo. Whereas IL-23, also a heterodimeric cytokine, is composed of a unique p19 chain linked to the p40 subunit. IL-23 is associated with promotion of both IL-17 and IFN-γ, suggesting that these mediators interact to induce severe colitis. Animal models, using the cell-transfer colitis model, showed that the development of colonic inflammation was apparently more dependent on IL-23 than IL-12 cytokines. Moreover, reports also identified IL-23 but not IL-12 as an essential mediator of intestinal inflammation. In contrast to previous results, studies on IL-23 suggested that IL-12 can contribute to intestinal inflammation, particularly in the absence of IL-23, possibly due to an exacerbated IL-12 response. These findings illustrate the complexity of immune regulatory interactions in the gut and suggest a potential diverse role for IL-12 and IL-23 in the control of acute and chronic intestinal inflammation. Therefore, the rationale of developing a neutralizing monoclonal antibodies targeting the p40 subunit, consists on the blockade on both IL-12/IL-23, cytokines presumed to participate on the perpetuation of an inflammatory cascade in the gut tissue [26–28].

The pivotal role of IL-23 in promoting intestinal inflammation via inflammatory mediators including IL-17A, is well described. In

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