Innovations in IBD treatment

Graham Cope, Honorary Senior Research Fellow, University of Birmingham, and Freelance Medical Writer, talks about treatment options for patients with Crohn's and UC

Inflammatory bowel diseases (IBD), particularly Crohn's disease (CD) and ulcerative colitis (UC), are chronic, disabling, and progressive diseases. Most traditional drug therapies provide symptomatic improvement (Bryant et al, 2015); however, they fail to prevent the underlying inflammatory process and have little effect on the disease course (Burger and Travis, 2011). The advent of anti-tumour necrotizing factor-alpha (anti-TNF-α) agents, such as infliximab and adalimumab, dramatically changed IBD treatment, resulting in fewer surgeries and hospitalizations, greater clinical remission, better mucosal healing rates, and a superior quality of life (Ha et al, 2015). The search for even better biological agents has produced interesting compounds, a few of which are in the pharmaceutical pipeline (Amiot and Peyrin-Biroulet, 2015).

Inflammatory mechanisms

Chronic intestinal inflammation can develop via different mechanisms, strongly suggesting that CD and UC are heterogeneous diseases with similar final pathways. IBD results from the failure to appropriately regulate nonspecific inflammation initiated by an environmental trigger. Normally, an individual can quickly clear infections of invasive enteric bacteria without long-lasting effect, but in genetically susceptible individuals, they respond to these pathogens with heightened immune responses and changes to the mucosal barrier, and proceed to chronic, relapsing intestinal inflammation. The enhanced immune response typically involves macrophage, neutrophils, T- and B-cells, and natural killer cells, which secrete a cocktail of growth factors, interleukins, leukotrienes, interferon, and cytokines, with TNF playing a large part in the inflammatory process (Sartor, 2006).

General management principles

The overall goals in the management of patients with IBD are to induce and maintain remission and prevent complications. This requires appropriate clinical management by a multidisciplinary IBD team.

For decades, medical treatment for IBD consisted of corticosteroids, typically prednisolone or hydrocortisone. While corticosteroids are excellent at inducing remission, maintenance therapy is problematic because the disease may become refractory and many side effects could develop (Talley et al, 2011).

The choice of treatment depends on disease activity and extent, as well as patient acceptability and mode of drug delivery. Disease activity is best confirmed (and infection excluded) before therapy is initiated or when response to therapy is slow. To optimize conventional therapy, it is important to carefully time the steps of treatment and explain the strategy to the patient (Burger and Travis, 2011). Common mistakes in conventional therapy include over prescription of mesalamine for CD, inappropriate use of steroids, delayed introduction, or under dosing with immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) and failure to consider timely surgery (Burger and Travis, 2011).

Targeting TNF

The proinflammatory cytokine TNF plays a key role in chronic intestinal inflammation that causes IBD. Hence, most biological agents aim to neutralise or antagonise TNF. The first drugs available in this class were infliximab and adalimumab, but more recently, golimumab has been released—a subcutaneous, fully human, anti-TNF antibody. It has general anti-inflammatory effects, and has good efficacy on aspects of IBD including clinical response, remission, mucosal healing, and improved quality of life (Amiot and Peyrin-Biroulet, 2015).

In IBD, the inflammatory process is characterized by leukocytic infiltration of the intestinal lamina propria (Lobatón et al, 2014), and recruitment of leukocytes from circulation into the site of inflammation could be vital in controlling the inflammatory cascade. This process involves several steps, such as capture of leukocytes by the endothelium, through the interaction of adhesion molecules, integrins, and leukocyte cell walls (Beniwal-Patel and Saha, 2014). Natalizumab is an IgG4 humanized monoclonal antibody that specifically antagonizes integrin, which induces and maintains clinical remission in CD; this drug is licensed in the US. Vedolizumab is a humanized monoclonal antibody that specifically antagonizes integrin, by inhibiting its binding to the gut mucosa. Vedolizumab has been approved for treatment of adult patients with moderately to severely active UC or CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist (Feagan et al, 2013).

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Altering intestinal microflora

Gut bacteria play a crucial role in the health of the human intestine and a disturbance of the delicate homeostasis is important in the development and maintenance of IBD. Hence, changing the bacterial ecosystem is an attractive approach in developing novel therapies. Antibiotics are not normally recommended for the treatment of UC and CD, except in cases of fistula or septic complications or pouchitis. Some small trials of rifaximin (semi-synthetic antibiotic based on rifampycin) have shown a beneficial effect; it is also unclear whether the antibiotic effect is due to the removal of specific pathogenic bacteria or a rebalance in the gut flora. Therefore, use of antibiotics is not generally recommended in the treatment of IBD considering the risk of antibiotic resistance (Talley et al, 2011).

Probiotics, or the use of live micro-organisms, to reestablish the normal flora has been investigated. One study with VSL 3 showed promise (Miele et al, 2009), but the improvement did not reach significance. Natura-α, which reportedly affects T-helper cells, proved positive in a small trial (Wang et al, 2012), but larger trials are required.

Biological agents in the pipeline

The majority of new molecules for the treatment of IBD aim to target T-cell activation, adhesion molecules, or pro-inflammatory cytokines. A novel approach for targeting TNF is through the generation of polyclonal antibodies using the patient's own immune system. TNF-Kinoid is an 'immunotherapeutic' produced from recombinant human TNF conjugated to a deactivated carrier protein. The administration of TNF-Kinoid theoretically prompts the production of neutralizing polyclonal antibodies against TNF (Delavallee et al, 2008). Clinical trials are ongoing with encouraging results regarding adverse events and clinical response and remission.

Another compound is HMPL-004, an extract from an annual herbaceous plant native to India and Sri Lanka. This has shown an ability to reduce the circulating levels of TNF and interleukin and interferon, and to inhibit T-cell proliferation and T-helper cell responses (Michelsen et al, 2013).

Pro-inflammatory interleukins (IL) are cytokines, and specifically IL-12 and IL-23 are thought to induce T-helper cell differentiation and other inflammatory actions. IL-12 and IL-23 are now being investigated as the targets for monoclonal antibody treatment. Ustekinumab is a monoclonal IgG1 antibody and seems to be effective in inducing a clinical and maintenance therapy (Sandborn et al, 2012). Tocilizumab is a fully humanized monoclonal antibody that blocks another interleukin. IL-6 too has shown promise (Singh et al, 2010).

Anti-adhesion molecules such as etrolizumab and natalizumab are monoclonal antibodies that bind to and deactivate specific integrin molecules and have been shown to be effective in trials in patients with moderate-to-severe active UC (Vermeire et al, 2014).

Gastrointestinal inflammation involves mast-cell degranulation, histamine release, and other cytokines and growth factors. Masitinib targets mast cells and prevents release of these pro-inflammatory mediators (Dubreuil et al, 2009).

Conclusion

While conventional treatments for IBD are excellent at reducing inflammation and inducing remission, the underlying cause of the disease is neglected. Anti-TNF agents that are successful in treating IBD reduce the burden of local and systemic inflammation, but are associated with an increased risk of infections. Numerous compounds are in the pipeline and various clinical trials are ongoing; while they offer new therapeutic options for these incurable diseases, they also help to understand the underlying causes that differentiate UC and CD and to explain the complex mechanisms involved in the inflammatory process of the gastrointestinal tract. GN

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