Inflammatory bowel disease (IBD), which includes both Crohn’s disease (CD) and ulcerative colitis (UC), affects approximately 1.4 million people in the USA [1] and results from a complex interaction between innate and adaptive immunity [2]. It is believed that aberrant innate immune responses to commensal flora play an important role in IBD pathogenesis [3]. Patients with IBD develop strong immune responses to common bacterial antigens that do not trigger an immune response in a normal host [3]. Controlling inflammatory responses to commonly encountered antigens presents a challenge to the mucosal immune system of patients with IBD. The basal state of mucosal immune suppression observed in healthy people is important to prevent a pathologic response to the constant presence of commensal flora and dietary antigens. While the immunologic tone of mucosa-associated lymphoid tissue in a normal host is that of hyporesponsiveness or suppression, the immunologic tone of the mucosa-associated lymphoid tissue in an IBD patient is that of activation [3]. The mechanisms responsible for the healthy tone of hyporesponsiveness in a normal host involve complex interactions between the intestinal epithelial cell of the GI tract and the underlying T lymphocyte in the lamina propria [3]. Intercellular communication in the gut mucosa occurs via a broad array of cytokines, some of which, such as TNF-α, IL-12 and IL-23, have been demonstrated to play a key role in fostering gut inflammation in patients with CD [4,5]. TNF-α is also found in increased concentrations in the blood, colonic tissue and stools of patients with UC [6,7]. TNF-α is a potent proinflammatory cytokine with pleiotrophic effects on cells of the innate and adaptive immune system. It promotes the production of additional proinflammatory cytokines (IL-1 and IL-6), upregulates the expression of adhesion molecules on vascular endothelial cells (vascular cell adhesion molecule and intercellular adhesion molecule-1) and mediates the secretion of tissue-altering enzymes (matrix metalloproteinases, collagenase and elastase) that alter tissue architecture [8].

Medical therapies that block TNF have changed the clinical management of chronic inflammatory disorders, including IBD. Since the initial report of the first successful use of...
TNF-α blockade in patients with moderate-to-severe CD in 1997 [9], many studies have focused on the delineation of the mechanisms of action of anti-TNF-α mAbs. Accumulating evidence suggests that not only soluble TNF-α, but also its precursor form, membrane TNF-α, is involved in the inflammatory response [10]. Membrane TNF-α acts both as a ligand by binding to TNF-α receptors, and a receptor that transmits outside-to-inside (reverse) signals back into the TNF-α-producing cells [10]. The newly recognized biological activities of membrane TNF-α as a receptor have been demonstrated in T cells, monocytes/macrophages and NK cells in humans [11,12]. Recent studies have suggested that different anti-TNF-α agents have variable effects against membrane TNF-α, possibly explaining their different biological efficacy in IBD. Thus, infliximab and adalimumab, but not etanercept, induce apoptosis and cell cycle G0/G1 arrest upon binding to membrane TNF-α-expressing Jurkat T cells, a T-cell leukemia-derived cell line [13]. In addition, IL-10 production is induced by infliximab but not etanercept in membrane TNF-α-expressing Jurkat T cells [13]. Despite these differences, clinical efficacy profiles of anti-TNF agents are unlikely to be solely dependent on their activity against the membrane TNF-α and other effects on the inflammatory network that are different between anti-TNF agents may determine their overall effectiveness in treating IBD.

A new approach to biologic therapy has been the development of inhibitors of various elements in the leukocyte adhesion process. The main targets of these new agents are the integrins α4β1 and α4β7, which interact with VCAM-1 and MAdCAM-1, respectively, to mediate interactions between leukocytes and endothelial cells [14]. Monoclonal antibodies, natalizumab and MLN0002 (vedolizumab), bind to and antagonize α4 and α4β7, respectively. These new therapies have provided another medical option for IBD patients who are unresponsive to conventional therapies and anti-TNF agents.

In the following sections, the authors will discuss key studies pertaining to the efficacy and safety of biological agents used in the treatment of CD and UC. They will also discuss new insights into the appropriate dosing and monitoring parameters of these drugs that may help achieve and preserve a sustained response to these agents.

**Anti-TNF therapy**

**Crohn’s disease**

**Infliximab**

**Inflammatory CD**

Infliximab (Remicade®, Centocor, CA, USA) is a IgG1 (murine [25%] and human [75%]) chimeric mAb targeted against TNF-α [15] and is given as an intravenous infusion. It was the first biologic approved for the treatment of CD. Studies over the past 15 years have documented the efficacy of infliximab (IFX) in inducing and maintaining remission in steroid-refractory, steroid-dependent and immunomodulator-refractory inflammatory CD, healing of complex fistula and preventing postoperative recurrence. In 1997, Targan *et al.* reported that a single infusion of IFX provided significant clinical and endoscopic benefit for patients with treatment-refractory moderate-to-severe CD [9]. Other early studies have shown similar success with IFX for the treatment of refractory CD disease (Hungary: 46.0% and Milan: 31.3%) [16,17].

Subsequent studies have demonstrated efficacy of IFX in the maintenance of remission in CD. The ACCENT I trial showed that maintenance therapy with either 5 or 10 mg/kg of IFX was more effective than placebo in sustaining clinical remission and sparing patients steroid use [8]. A separate analysis of the ACCENT I study revealed that scheduled IFX treatment resulted in a greater improvement in CDAI and mucosal healing at 54 weeks, fewer surgeries and hospitalizations, and a lower proportion of antibody formation, as compared with episodic treatment [19]. A subsequent study from Belgium showed that 68% of patients who responded to IFX achieved mucosal healing while on long-term maintenance IFX. In addition, mucosal healing was associated with an improved long-term outcome of the disease, such as a decreased need for hospitalizations and major abdominal surgeries [20]. It has been shown in a population-based cohort before the era of biologic therapy that mucosal healing at 1 year after diagnosis is predictive of reduced subsequent disease activity; however, to date, IFX is the most potent inducer of mucosal healing [21].

Although IFX is an effective drug for the induction and maintenance of remission in CD, a significant proportion of patients experience loss of response (LOR) and flare of symptoms. Definitions of LOR vary: a recent ECCO workshop defined LOR as a 70-point elevation of CDAI, whereas others define LOR as the need for IFX dose escalation, IFX cessation or surgery [22,23]. In the ACCENT I trial, the median time to LOR was 38 weeks for IFX-treated patients. A subsequent study of prolonged IFX therapy from a single center in Belgium revealed that after a median follow-up of 55 months, 63% of patients had sustained benefit and 22% experienced LOR despite an increase in dose and shortening of dose intervals [24]. A more recent study from a single center in Spain reported the annual risk of LOR to IFX to be 12% per patient-year of treatment (n = 309; mean follow-up: 41 months) [25]. A meta-analysis by the same group evaluating LOR for IFX in 16 studies with a total of 2236 patients found that 37% lost IFX response with an annual risk for LOR to IFX of 13% per patient-year [26].

The administration of IFX leads to highly variable serum concentrations [16]. This variability may influence clinical response in CD. The ACCENT I trial has reported that 50% of patients who receive a single dose of 5 mg/kg IFX have undetectable levels at week 14. It has also been shown in a cohort of 105 CD patients that the rates of clinical remission and endoscopic improvement are higher in patients with a detectable trough serum IFX level compared with patients in whom serum IFX was undetectable [27]. Despite the association between low trough levels and LOR, routine measurements of IFX drug levels to guide dosing are not yet being performed, as prospective controlled trials for this practice are lacking. Possible reasons for low trough levels and LOR to IFX will be discussed in the ‘Antibodies to monoclonal drugs’ section of this review.
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