Review Article

Biologics for Ulcerative Colitis: Status of the Art and General Considerations

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Abstract

Background: Expanding over Crohn's disease in the Far East, and easily biased to chronicity, ulcerative colitis (UC) continues to pose a challenge. Traditional remedies have been based on control of inflammation and immune suppression, effected by such classic drugs as mesalamines, corticosteroids, and thiopurines. However, these molecules have long proven unable to fully control the disease or modify disease history, leaving an alternative fully desirable.

Objectives: In this study, we aimed at highlighting the indications for biological therapy in UC.

Methods: Literature review.

Results: Recently, it has been demonstrated that the proinflammatory cytokine tumor necrosis factor (TNF) plays a significant role in UC, opening a way for anti-TNF biologics to join the therapeutic arsenal. These monoclonal antibodies, now available as hybrids or fully human preparations, are able to attain at least 50% response rate of refractory UC. However, primary non-response amounts to 20% - 40%, and loss of response to 40%. Optimization protocols allow for biologic molecule switching (disease symptoms, antibody positive) or replacement with another drug class (symptoms but no antibodies). Infectious/neoplastic /autoimmune toxicities together with high costs continue to be a problem (52%).

Conclusions: These results warrant further therapeutic leaps forward: personalized therapy plans based on the patiens' genetic profile, and pre-emptive measures based on people's education to modify diet and life habits.

Keywords: Inflammatory Bowel Disease, Biologics, Immune Suppression

1. Background

Ulcerative colitis (UC) makes one of the two phenotypes of the category of inflammatory bowel diseases (IBD) (1). UC is confined to the colonic mucosa, histologically presenting as a kind of Arthus-like phenomenon (2), with immune aggregates attracting cells and complement factors around an inflamed vessel (vasculitis). In the Western world, the incidence of UC is estimated in the range of 15.0 per 100,000 persons per year (3). UC significantly tends to chronicization, owing to progressive accrual of inflammatory cells to the inflamed sites, and antigen presentation by non-professional presenting (dendritic) cells, which prove resistant to apoptosis (4). The majority of the UC cases may run a relatively benign course, needing steroids (see below) in only 30% of the cases (5); in 10% - 15% of the cases, the disease may behave as a fulminant affection (6).

Capable to inhibit the main proinflammatory mediator NF-kB (7), mesalamines are the mainstay for treatment of mild-moderate UC. A recent Cochrane analysis (8) revealed a 30% therapeutic gain over placebo for all of the available formulations. Up to 60% of the moderate-severe presentations need steroids to be driven to remission, and the remaining 40% may require cyclosporine (9) (see be-

low). Those cases treated with steroids do need thiopurines for the best maintenance regime. In our hands, thiopurines maintained remission in 80% of the cases of severe UC at 1 year (10).

Although satisfactory, these options have left desire for some improvement, specifically an increase in the percentage of the responders and an attempt to modify the disease history.

In the last two decades, the investigators and caretakers have focused on the proinflammatory tumor necrosis factor cytokine (TNF) (11), as a possible target for therapeutic antibodies, in the treatment of difficult UC. Indeed, the physiopathological role of TNF in the pathogenesis of UC is believed to be sustained by several arguments, which are as follow: (a) An increased production of TNF has been shown in colonic mucosa, stools, rectal dialysates, and plasma from active UC patients; (b) Soluble TNF receptors have been highlighted in the urine of these patients (12); (c) The UC of cotton-top tamarine (an animal model that develops spontaneous UC) seems to be restraint by treatment with anti-TNF molecules (13).

In brief, the anti-TNF monoclonal Infliximab (Remicade®) was approved by the FDA for the treatment of fistulizing and steroid dependent IBD in 1998 (14). Classic ad-

ministration schedules require injecting 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks, with occasional individualization changes. Several open studies since then gave mixed results. The two controlled multicenter studies (ACT-1 and ACT-2) in 2005 (15) were defined as the demonstration of the efficacy of Infliximab in the treatment of moderate/severe UC.

2. Data Acquisition

Severe steroid refractory UC has been considered the chief indication for infliximab.

3. Results

An initial randomized controlled study showed, for the treated patient subset, a 3-yr colectomy rate of 50% as opposed to a 76% for the placebos (16). Variable colectomy figures (20% - 75%) were then reported in subsequent studies (17-20). Data on long-term protection from elective colectomy after leaving Infliximab are mixed. Some studies have indicated endoscopic deep remission as the harbinger of long-term response, but others have not. Moreover, retreatment after relapse was successful only in 54% of the cases (21).

The subsequent release of other anti-TNF molecules (adalimumab, golimumab) and the possibility to detect specific antibodies to the anti-TNF in serum have opened new avenues of knowledge (22).

After induction of remission, approximately 40% of the patients lost response (23). This partially depended on the rise of antibodies to the formulation. The available countermeasures were as follow: 1) prohibiting smoking; 2) dose optimization (dose increased or given more frequently); 3) addition to a thiopurine; a 4) switching to another anti-TNF. Experience has shown that some 50% - 88% of the subjects may respond to dose increase (24). Switch to a third party drug may be specifically promising if vedolizumab (anti-integrin alpha-4/beta-7) is used (25).

Safety issues are not negligible for antiTNF strategies and may be one major cause of forced withdrawal. Toxicity issues may include: 1) infectious accidents such as pulmonary TB and HEP-B virus reactivation; 2) arousal of autoimmune disease including lupus; 3) allergic reaction (26, 27).

4. The Highlighted Results, Targeted discussion, and Recommendations

Having laid down these data, we can now attempt to answer a few of the most frequently asked questions.

4.1. General Strategic Issues

A. Indications and candidate patients to anti-TNF strategies (28): A1 severe steroid-refractory UC, if cytomegalovirus and Cl difficile are negative; A2 severe steroid-dependent UC; A3 severe axial or peripheral arthropathy; A4 severe contraindications to steroid therapy

B. When to start anti-TNFs (29): A major variable in the timing to begin patients on anti-TNF depends on whether the caretaker physician is keen at adopting a top-down strategy.

C. Assessing response (30): The toronto consensus conference of 2015 has established that the goal of therapy is complete remission, defined as both symptomatic and endoscopic remission, without steroid therapy. Endoscopic response has also been defined elsewhere as "deep remission".

D. How long the therapy should be continued (exit strategies): on practical grounds, this may depend on the timing of response loss. For example, the Charm (31) and Extend (32) studies have continued adalimumab for 4 years, ending up with a remission maintenance of 30%.

4.2. Failure

A. Primary non-response (22): This is expected to occur with a frequency of 10% - 40%.

B. Secondary loss of response is defined as reappearance of clinical symptoms in already asymptomatic patients. According to Ben-Horin and Chowers (33), this may be encountered in 23% and 46% of the patients receiving infliximab and adalimumab, respectively. Failures have of course stimulated search of treatment optimization, and a relevant algorithm is illustrated in the next point. A recent study (34) has recorded a 60% relapse rate despite achieving deep remission.

4.3. Treatment Optimization

A. Combination therapy: on theoretical grounds, it may be easily anticipated that a purine immune suppressant synergize with an anti-TNF biologic, mostly by hindering the formation of antibodies to the biologic formulation. Indeed, a trial of 2014 has assessed that such combination strategy is superior to either drug alone in terms of achievement of endoscopic remission (35). Several experts have interpreted these results with caution, recommending the a-priori addition of a thiopurine only in cases of persistence of failure despite full attempts at optimization.

B. William Sandborn presented a simple optimization schedule, which is as follows (36):

1. Disease activity symptoms +antibodies to the biologic: switch to other TNF inhibitors

2. Symptoms + low antibody titers: increase dose

3. Symptoms despite no antibodies and good drug concentrations: perform endoscopy, and, if the disease was active, consider abandoning the anti-TNF strategy

C. Post-operative use of anti-TNFs: there is a scanty literature on this issue (37). A paper of 2014 reports an increased indication for anti-TNFs in pediatric patients who had undergone restorative proctocolectomy and ileal pouch.

5. Conclusions

The overall message from these figures is that the biologics have opened a promising avenue in the treatment of IBD and UC, yet they remain problematic molecules and have failed to prove their ability to actually modify the natural history of IBD. In addition, one has to duly note that UC remains curable with colectomy, and no experimental treatment is justified if it places the patient's survival in jeopardy in the face of a definitive (and safe) surgery.

6. The Future

In our opinion, the future of the treatment strategies for UC and IBD in general is centered on two pivots: One of an immediate endeavor, and the other being a sort of pre-emptive policy.

As to the first one, the continuously refining techniques of molecular profiling should be translated into IBD clinics and research, with the wishful thinking of providing the IBD caretaker with a sort of personalized map to indicate the best fitting treatment and drug choice for each patient (38, 39).

An example of pre-emptive policy against IBD: The role of diet. As this issue was outside the sphere of this paper, we only provide a superficial coverage, but refer the readers to a couple of recent valuable publications (40, 41).

At the midst of the past century, infectious diseases dropped dramatically, owing to better sanitation and massive antibiotic use. However, "Western" (immune/autoimmune) disorders took place rapidly including diabetes, lupus, arthritis, and IBD. The rapid IBD rise could not be explained in terms of genetic mutations (these would take longer). However, a significant change of variegated conditions might be invoked through abandoning countryside life in favor of living in metropolis cities, working in artificially lighted environment, and working on night shifts.

These conditions forced feeding at times predefined by work necessity, but diet also changed in terms of composition, and preference becoming biased towards refined sugars and proteins, and industrially prepared food that is nicely flavored, nice to look at, and easy-to-store. All these changes, forced by directional selection and taking the place of stabilizing selection, hit the human beings as a whole and the microbiome in particular. The microbiome could hardly keep pace with driving forces such as antibiotic use, prevalence of sugar diets, changed feeding times, and stressful conditions.

The human microbiome and its mutations might provide the factors linking in a logical manner to life-style changes and the mutated epidemiologic figures of IBD. Animal studies clearly indicate that mice genetically permissive for IBD (IL-10 -/-) fail to develop the disorder if kept germ - free. Moreover, the introduction of genetically engineered bacterial species may prove therapeutic for gut inflammation. Furthermore, the microbiome in IBD is less abundant, and most importantly, less diverse.

To this end, the observation that specific microbiome species that produce SCFA are reduced in IBD has been seminal. Short-chain fatty acids (SCFA) are the primary fuel for the correct thriving of colonocytes and might provide crucial barrier functions.

This knowledge might recommend that future interventions be directed toward education to follow diets that favor SCFA production, and/or addition of prebiotics that boost the growth of SCFA-producing bacterial genera.

Combinatorial analysis of the 3 factors of diet, microbes, and host genetics will be mandatory to formulate both prophylactic and therapeutic approaches that are accepted by the general population, but also individually, in the light of the personalized medicine referred to in the preceding paragraph.

Acknowledgments

Footnote

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