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New therapeutic approach in inflammatory bowel disease

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Abstract. – In the last decade, biologic agents, in particular infliximab and adalimumab, have deeply changed the therapeutic armamentarium of inflammatory bowel disease (IBD). However, these drugs have a number of contraindications and side-effects that physicians should know so to avoid and eventually manage them. Another important issue is the early introduction of immunomodulators and biologics in the therapeutic algorithm of IBD, the so called "top-down" approach compared to the traditional "step-up" approach. In this review, the indications to the use of anti-TNF-α molecules in IBD are briefly reported and the potential benefits and disadvantages of a more aggressive approach are discussed.

Key Words:

Inflammatory bowel disease; TNF-α; Infliximab; Adalimumab; Biologic agents.

Introduction

Inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD), affects 1 to 2 million people only in the United States (US), or about 100 cases per 100,000 population. IBD are chronic diseases with a heavy impact on patients' quality of life and an high morbidity. The aetiology of IBD is unknown, even if in the last decade many of the factors involved in their pathogenesis have been identified and well characterized. Today, there is general agreement among investigators that the external environment, the patient's genetic makeup, intestinal microflora, and the immune system are all involved and functionally integrated in the generation of the persistent inflammatory process that characterizes IBD[1]. This advanced knowledge in the molecular processes implicated in the pathogenesis of both CD and UC has led to the discover and use in clinical practice of new drugs, the so called "biologic agents" with well-defined molecular targets. Among biologics the most known and currently used are the anti-TNF-α monoclonal antibodies infliximab (IFX) and adalimumab (ADA). Thus, the objective of this article is to supply a synthetic update on the new therapeutic options for IBD, in particular the available anti-TNF-α drugs and, to compare the traditional therapeutic approach for CD patients with moderate-severe active disease (step-up approach) to a more aggressive therapeutic approach based on an early introduction of immunomodulators and biologics (top-down approach).

Indications and Contraindications to the Use of Anti-TNF-α in IBD

Infliximab is a chimeric monoclonal antibody, constituted of 75% human IgG1 isotype and 25% of murine component. Since its first launch, in 1998, over one million of patients worldwide have been treated with IFX. They were affected by IBD other than rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), and psoriasis.

IFX was first approved in 1998 for CD. In particular, IFX was indicated for patients with luminal steroid-resistant or -dependant CD or with fistulizing disease. After some years IFX was approved both in the US and Europe also for maintenance of both luminal and fistulizing CD. Recently, the use of IFX was extended to active moderate-to-severe UC resistant to conventional therapy or steroid-dependant. However, the use of IFX has a number of well known contraindications, absolute and relative (see Tables I and II), and side-effects (Table III). Thus, physicians who prescribe IFX need to know not only the indications to its use but also the more prevalent adverse events in order to prevent and, eventually to manage them. In particular, active or latent

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Table I. Absolute controindications to the use of infliximab.

- Active infection, acute or chronic
- Solid cancer or haematological malignancy, diagnosed within the last 5 years, with a potential for progression
- Heart failure, class III or IV (NYHA)
- Demyelinating disease

infective diseases have to rule out before to start IFX treatment. Also concurrent or recent neoplasia and severe heart and neurological diseases represent absolute contraindications to the use of IFX and other anti-TNF- α drugs. The most frequent IFX side-effects are infective events generally of mild entity but sometimes severe and life-threatening such as tuberculosis, systemic mycosis, bacterial sepsis, etc. Also infusion reactions may occur, fortunately, most of them don't require IFX suspension even if the immunogenicity of IFX can led to formations of antibodies towards the murine component of IFX that may contribute to the loss of response. Another important safety issue is the possible increased risk of neoplasia, lymphoma in particular, although several reports didn't find an higher risk of lymphoma in CD patients in treatment with IFX when compared to CD patients not treated with IFX[2]. However, the occurrence of hepatosplenic T-cell lymphoma (HSTCL) in young patients on IFX plus concomitant azathioprine seems to be a real risk even if principally attributable to the immunosuppressant use[3]. Moreover, some of the patients treated with IFX experience a loss of efficacy over time or become intolerant to IFX.

ADA is a human recombinant antibody (100% human IgG1 isotype) that is effective in inducing and maintaining remission in patients with CD who are both "naive" to infliximab[4-5] or that cannot tolerate or became unresponsive to IFX[6]. ADA is administered subcutaneously and does not require endovenous route as for IFX. Up to now, ADA is approved only for CD (other than

Table II. Relative controindications to the use of infliximab.

- **Situations associated with a high risk of infection:** latent untreated tuberculosis, chronic infection, uncontrolled diabetes
- **Cancer diagnosed more than 5 years ago, treated, and considered cured**
- **Premalignant lesions**, eg.,: polyps in the colon or urinary bladder, cervical dysplasia, myelodysplasia
- **Pregnant or breastfeeding woman**

Table III. Side-effects of infliximab therapy.

- Infusion reactions: immediate or delayed
- Infections: respiratory tract and urinary tract infections, cellulites, tuberculosis, opportunistic infections (histoplasmosis, Pneumocystis carinii infection, Cytomegalovirus infection, nocardiosis, listeriosis, aspergillosis, etc.)
- Neoplasia
- Hepato-splenic T-cell lymphoma (HSTCL)

for rheumatologic and dermatological disease) with the same indications of IFX. The contraindications and the side-effects of ADA are similar to those reported for IFX, even if being ADA a fully humanized antibody it should be less immunogenic than chimeric monoclonal antibody and, consequently, should give less allergic and autoimmune phenomena. Moreover, reactivation of latent tuberculosis and the onset of other opportunistic infections seems to be less frequent with ADA than with IFX[7].

Top-Down Versus Step-Up Approach in CD Patients

Recent debates have centered on where biologics should be positioned within the current treatment strategy for CD so as to maximize efficacy while balancing risk. The therapeutic strategy actually used for CD by the majority of gastroenterology has been called a "step up" approach. It consists in treatment progression from salicylates, antibiotics, and topical and/or systemic steroids through immunomodulators and culminates with anti-TNF therapy (Figure 1). However, this strategy focuses on a limited hori-

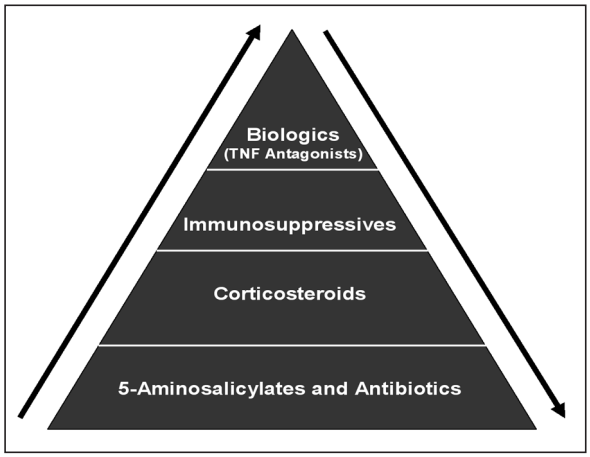

Figure 1. Step-up versus top-down approach.

zon time and symptomatic relief not considering the possibility of modify the natural history of the disease so to avoid disease progression towards more complicated form because of inadequate response to medical therapy. Indeed, a recent study has tested the hypothesis that positioning immunomodulators and biologics early in the IBD treatment algorithm ("top-down" strategy) may result in superior outcomes compared with the current step-up strategy, in which these agents are used only in patients failing conventional therapies or who are steroid-dependant[8]. The potential advantages of "reversing" our current therapeutic pyramid/algorithm for the treatment of CD include early disease stabilization and disease modification, minimization of complications such as strictures and fistulae that lead to the need for surgery, reduction of postoperative recurrence, and avoidance of the ubiquitous complications of corticosteroid therapy. However, the available data regarding the superiority of the top-down approach when compared to the step-up strategy are still limited and to date several factors limit the use of biologics as primary therapy for IBD patients: first of all safety profile of these drugs and then the costs of an extensive use of this strategy to all IBD patients. Moreover, we must remember that about 50% of all IBD patients never require steroids and, consequently, first-line treatment with biologics and immunomodulators in this group exposes patients to potential toxicity or immunogenicity without the benefit of a potentially changed natural course in the long run[9].

However, newer anti-TNF-α agents, such as adalimumab and certolizumab pegol, have the potential to reduce the risk of immunogenicity and the associated infusion reactions and loss of response, as well as reducing autoimmunity associated with IFX therapy. Finally, it is unlikely that one strategy will be best for all patients given the underlying heterogeneity of CD presentation and severity. Thus, the challenge will be to identify patients who will develop a more aggressive course of disease and have a high response rate to immunomodulators and biologics.

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