

Chapter

Biological Therapy for Inflammatory Bowel Diseases: Screening Prior to Initiating and How to Proceed When Surgery Is Necessary

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Abstract

Biological therapy has revolutionized the management of inflammatory bowel disease (IBD) in the last 30 years. However, these drugs have side effects and adverse events. Before starting this therapy, it is necessary to screen for specific infectious diseases and monitoring protocols. Screening for human immunodeficiency virus, hepatitis C, hepatitis B, and *Mycobacterium tuberculosis* infections must be included. In addition, vaccination should be checked and updated if necessary. Despite the advent of biological therapy, a significant number of patients with IBD will need surgery in their lifetime due to either clinical intractability or disease complications. Many of them will be on biological therapy, and there is a considerable controversy about adverse effects of biologics on surgical outcomes. In this chapter, we will approach the screening required to start this therapy and how to proceed when surgery is necessary in these patients.

Keywords: inflammatory bowel disease, surgery, biologic agents, complications, infectious diseases, vaccines

1. Introduction

Biological therapy brought a better control of inflammatory bowel diseases (IBD). However, its use requires specific care before the beginning and during the treatment. Some essential points in its management have raised discussions.

We address the needs before starting the biological therapy and how to proceed when surgery is required. A brief review of what is necessary before the use of these drugs is also provided.

The management of other immunosuppressive agents such as corticosteroids, azathioprine, 6-mercaptopurine, and methotrexate is not covered in this chapter.

2. Pre-exposure biological therapy evaluations

The general recommendations include screening patients for risk factors of infection [1]:

- Comorbidities (e.g., transplant history, malignancy, renal or liver failure, diabetes mellitus)
- Age
- Occupation
- History of travel to areas of endemic diseases
- High-risk sexual activity, drug abuse
- Exposure to tuberculosis
- Blood transfusion

Patients receiving treatment with therapeutic monoclonal antibodies (specifically the tumor-necrosis-factor alpha inhibitors) are considered immunodeficient [2]. Therefore, before the onset of biological therapy, we should screen for some diseases, and the patients should be properly immunized [3–5].

Screening for human immunodeficiency virus infection (HIV), hepatitis C (HVC), hepatitis B (HVB), and *Mycobacterium tuberculosis* infection for all patients must be performed prior to starting biological therapy [1, 4–6].

Because of the risk and the severity of infections, which are increased in HIV-infected patients receiving biological therapy, they should be closely monitored. Biological therapy is not contraindicated in HIV-infected patients [4].

Screening of HVC in some European countries is not recommended because of its low prevalence and the fact that patients with HVC can be treated with biological therapy [5]. However, immunomodulators may influence active chronic HVC infection and may worsen liver function when concomitant infection with hepatitis B (concomitant HVB and HVC infection is common in some regions of the world) [4].

Every patient with hepatitis B negative tested (HBsAg, anti-HAbs, and anti-HBcAb negatives) should be vaccinated before starting biological therapy. One to two months after the last dose of vaccine, patients should have their serological response evaluated. If infection is present by testing before vaccination, other specific tests should be performed, and the patient should be evaluated by a specialist for the need of treatment. The importance of care in relation to HVB infection consists in the fact that reactivation of HBV is a well-described complication of immunosuppression [4, 5, 7].

One infectious agents which should get more attention before the beginning of the biological therapy is *Mycobacterium tuberculosis*, because the reactivation of latent tuberculosis is increased and more severe in patients who follow this therapy. Proper latent tuberculosis search is performed by an assessment of an exposure history, skin test (PPD-tuberculosis skin test), interferon gamma release assay (IGRA), and chest X-ray, according to local prevalence and national

recommendations. Complete therapeutic regimen for latent tuberculosis must be initiated if identified after the screening examination and the biological therapy should be delayed [4, 5]. This full latent tuberculosis investigation can be modified or even indicated only if some exposure is suspected depending on where the patient lives. In this case, regional guidelines for prophylaxis must be followed. Only 22 countries worldwide represent 80% of the world's incidence. Therefore, local variations in the tuberculosis screening are accepted [4–6, 8].

If results of IGRA test or PPD are negative, they should be repeated, but there is no consensus as to how long [5].

Despite the variations in relation to screening for latent tuberculosis, when an alteration in the PPD test (≥ 5 mm) is found, the prophylaxis with isoniazid or appropriated antituberculous therapy must be initiated and maintained for 6 months. After at least 4 weeks with the use of the medication, we can initiate biological therapy [6].

3. Vaccination

It is worth noting that the patient's entire history of vaccination must be checked. If they did not receive the vaccines, they must be updated. Attention should be given, also to the recommended waiting period between each vaccine and the initiation of therapy.

In addition to the hepatitis B vaccine, the patient should also receive the following vaccines before starting the treatment with biological therapy [4–7, 9]:

- Varicella zoster virus (VZV)—if lacking clear history of chickenpox, shingles or if past vaccination history is uncertain
- Tetanus and diphtheria toxoid—every 10 years
- Human papilloma virus—according to national guidelines
- Zoster vaccine—for immunocompetent individuals over 60 years old
- Influenza virus—annual vaccination for all patients
- Hepatitis A—in endemic areas
- Pneumococcal (PPSV 23 and PCV13 vaccines)—every 3–5 years
- Meningococcal—for certain at-risk individuals (college students living in residential housing, military recruits, and immunosuppressed patients like asplenia, HIV, and complement deficiency)

It is important to emphasize that immunosuppressed patients do not respond properly to immunization. In addition, patients receiving biological therapy cannot be vaccinated with live attenuated virus (varicella zoster, yellow fever, measles, mumps, and rubella) [9].

A brief algorithm for preparing the patient for biological therapy is outlined in **Figure 1**.

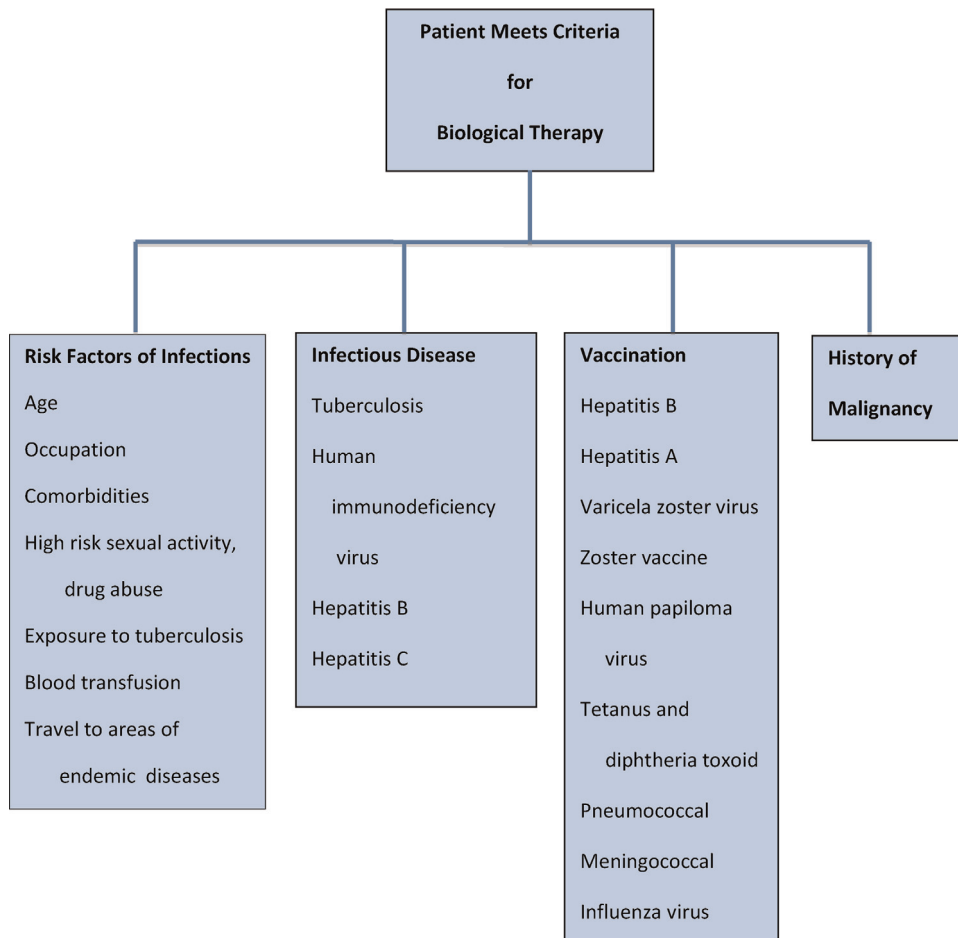


Figure 1.
Algorithm for preparing the patient for biological therapy.

4. Biological therapy and surgery

When the screening and prophylaxis prior to initiating biological therapy involve numerous details regarding each disease that should be treated or prevented, the issue regarding biological therapy use and performing surgery can be even more complex. This complexity is due to the difficult analysis of patients since the groups submitted to surgery are extremely heterogeneous.

Despite the increasing number of available biological agents available, many patients will require operation due to intractability or complications of IBD. In a systematic review and meta-analysis of population-based studies, Frolkis et al. [10] showed that the risk of intestinal surgery among patients with IBD has decrease over the past six decades. They concluded that the risk of surgery in Crohn's disease after 1, 5, and 10 years of diagnosis was 16.3, 33.3, and 46.6%, respectively, and in ulcerative colitis was 4.9, 11.6, and 15.6%, respectively.

In this way, many IBD patients will be on biological therapy when surgery is indicated. Literature data are conflicted with regard to the preoperative management of biological therapy in IBD surgery. Several large single-center studies and systematic reviews have found an increased risk of infectious complications with the use of anti-TNF preoperatively [11–14], whereas others have not [15–20].

These inconsistent results may be due to single institution experience, different duration of biological therapy, different periods between the last biologic dose and surgery, and concomitance with use of immunosuppressive agents and besides, may be a reflection of the severity of the disease and not the biological itself [16, 18, 21, 22].

Most studies use a 3-month cutoff to include patients in the anti-TNF group, but the serum level of the drug should also be taken into account [22]. Lau et al. [23] observed in their study that 53% of the IBD patients using preoperative anti-TNF had no detectable drug level at the time of surgery and it was more frequent in the ulcerative colitis group.

Regarding ulcerative colitis, the results are also conflicting with some studies showing increase in postoperative complications [24], while others show no association in preoperative anti-TNF therapy and increased risk of infectious and noninfectious complications after surgery [25].

Lightner et al. [26], in a retrospective multicenter cohort study, observed that IBD patients (Crohn's disease and ulcerative colitis) treated with vedolizumab had increased risk of postoperative surgical site infection and mucocutaneous separation of the diverting stoma as compared with anti-TNF-treated patients. They studied 146 patients who received vedolizumab 12 weeks before abdominal surgery and 289 patients who received anti-TNF therapy. However, two systematic reviews and meta-analysis [27, 28] did not find increased risks of postoperative complications with the use of vedolizumab when compared to either preoperative anti-TNF therapy or no biological therapy. Studies regarding the use of ustekinumab comparing with anti-TNF therapy also demonstrated no increase in the risk of postoperative complications [29, 30].

The occurrence of infectious and noninfectious complications after surgery in patients with IBD depends on several factors besides biological therapy. Among them one can mention the concomitance of the use of other medications, especially corticosteroids; the very severity of the disease; anemia, marked malnutrition in these patients, and smoking which greatly influence the occurrence of these complications [31]. Literature dates are conflicting, and in most studies, the patients and disease are heterogeneous. In addition, the time of exposure to the biological, the

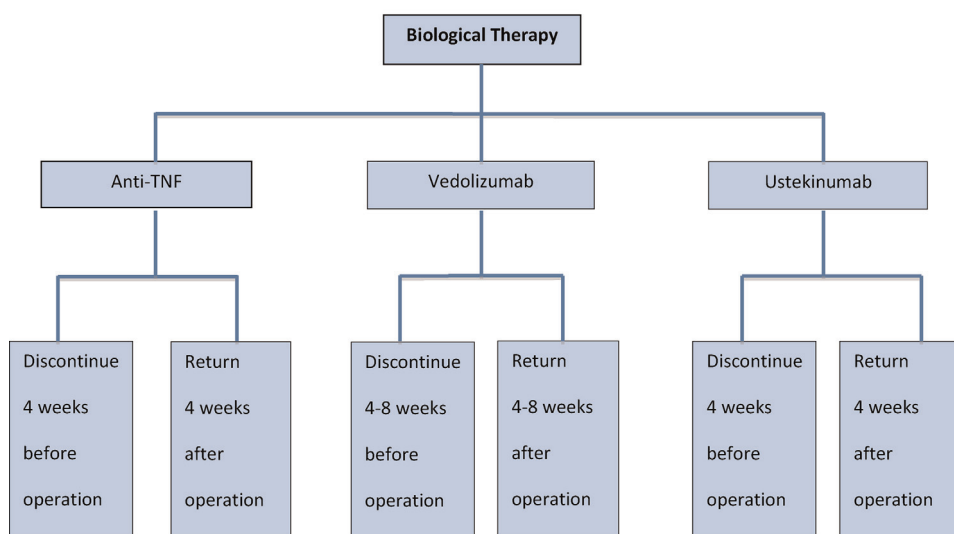


Figure 2. Biological therapy and surgery. Source: Adapted from Lightner AL. Perioperative management of biologic and immunosuppressive medications in patients with Crohn's disease. *Dis Colon Rectum* 2018;61:428-31.

interval between the last dose and the surgery, the serum level of the medication, and drug pharmacokinetic should be considered.

For patients who are receiving biological therapy and will undergo abdominal surgery, we should consider [32] the following:

- Discontinue the medication 4 weeks before operation for anti-TNF- α and ustekinumab and 4–8 weeks before for vedolizumab.
- The medication should be reintroduced after 4 weeks, if necessary.
- For urgent situation, there is no need to delay the operation. The increased risks of infectious complications do not outweigh the risk of delaying surgery.
- Consider derivative ileostomy in emergency surgery and severely malnourished patients (serum albumin < 3 g/L, body weight loss > 10%) and/or concomitant use of corticosteroids (**Figure 2**).

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