

Received: 2014.01.10
Accepted: 2014.01.21
Published: 2014.03.26

A guide to preparation of patients with inflammatory bowel diseases for anti-TNF- α therapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEFG 1 Júlio Maria Fonseca Chebli
ABEF 1 Pedro Duarte Gaburri
BDEF 1 Liliana Andrade Chebli
BDEF 1 Tarsila Campanha da Rocha Ribeiro
AEF 1 André Luiz Tavares Pinto
ABDEF 2 Orlando Ambrogini Júnior
ABDEF 3 Adérson Omar Mourão Cintra Damião

1 Division of Gastroenterology, Inflammatory Bowel Disease Center, Federal University of Juiz de Fora, Juiz de Fora, Brazil
2 Division of Gastroenterology, Federal University of São Paulo (UNIFESP), School of Medicine, São Paulo, Brazil
3 Laboratory of Medical Investigation (LIM 07), University of São Paulo Medical School, Hospital das Clínicas, São Paulo, Brazil





Corresponding Author: Julio Maria Fonseca Chebli, e-mail: chebli@globo.com

Source of support: Dr. Julio Maria Fonseca Chebli is the recipient of a grant from CNPq, Brazil; this study was partly supported by a clinical research fund from the CNPq and FAPEMIG, Brazil

Current therapy of moderate-to-severe inflammatory bowel disease (IBD) often involves the use of anti-tumor necrosis factor alpha (TNF- α) agents. Although very effective, these biologics place the patient at increased risk for developing infections and lymphomas, the latter especially when in combination with thiopurines. Appropriate patient selection, counseling, and education are all important features for the successful use of anti-TNF- α therapy. A thorough history to rule-out contraindications of this therapy and emphasis on monitoring guidelines are important steps preceding administration of anti-TNF- α agents. This therapy should only be considered if a recent evaluation has established that the patient has active IBD. In addition, it is important to exclude disease mimickers. Anti-TNF- α agents have been considered to present a globally favorable benefit/risk ratio. However, it is important that in routine practice, initiation of anti-TNF- α therapy be carefully discussed with the patient, extensively explaining the potential benefits and risks of such treatment. Prior to starting anti-TNF- α therapy, the patients need to be screened for latent tuberculosis, hepatitis B virus infection, and (usually) hepatitis C virus and HIV infection. Vaccination schedules of IBD patients should be evaluated and updated prior to the commencement of anti-TNF- α therapy. Ordinarily, immunization in adult patients with IBD should not deviate from recommended guidelines for the general population. With the exception of live vaccines, immunizations can be safely administered in patients with IBD, even those on immunosuppressants or biologics. The purpose of this review is providing an overview of appropriate steps to prepare patients with IBD for anti-TNF- α therapy.

MeSH Keywords: **Inflammatory Bowel Disease • Ulcerative Colitis • Agents, Biological**

Full-text PDF: <http://www.medscimonit.com/download/index/idArt/890331>

 5787  7  1  72

Background

The approach to patients with inflammatory bowel diseases (IBD) has changed remarkable over the last decade with the concept of treating the illness earlier with use of immunomodulators and anti-tumor necrosis factor alpha (TNF- α) therapies with the goal of altering the progressive and destructive course frequently observed on IBD [1,2]. Indeed, accumulating evidence suggests that anti-TNF- α agents, by promoting mucosal healing, may potentially modify the natural course of the disease by decreasing the need for surgery and reducing hospitalization rates as well as prolonging steroid-free clinical remissions [1,3]. Nonetheless, with increasing use of these more aggressive therapies comes the concern of cost and safety, including risk of opportunistic infections and neoplasia, which are largely preventable.

Currently, 4 anti-TNF- α therapies are available for treatment of patients with IBD. These agents are infliximab, adalimumab, certolizumab pegol, and golimumab. Although there are differences in routes and timing of administration of these drugs, the pretreatment evaluation protocol is similar regardless of the biologic agent used. For a variety of other immunosuppressants (e.g., azathioprine, 6-mercaptopurine, and methotrexate), the same considerations also apply, and the principles that will be disputed in this article can be used for treatment with these drugs. Nevertheless, particular precautions associated with each of these immunomodulators should be evaluated prior to initiating treatment. Herein, we review the preparation of the IBD patient for biologic therapy (Table 1), which is a pivotal issue for achieving the final aims of improving the patient's risk/benefit ratio and outcome.

Identifying the Appropriate Patient for Anti-TNF- α Therapy

Who should receive anti-TNF- α agents?

The decision to start anti-TNF- α therapy in patients with IBD is based on several factors: severity of disease, co-morbidities, possible benefits and risks, and evaluation of direct and indirect health care costs.

Traditionally, a step-up approach has been used in anti-TNF- α therapy as a late option before surgery. Thus, anti-TNF- α agents are indicated for moderate-to-severe IBD refractory to systemic steroids or an immunosuppressant, and in cases in which steroids are contraindicated or not appropriate [4]. Despite this conventional therapeutic strategy, no significant change has occurred in the natural course of IBD [5]. Hence, at least for Crohn's disease (CD), a new therapeutic avenue to change the course of this chronic disabling condition has emerged. Indeed,

Table 1. Suggested practice steps for preparing the patient with inflammatory bowel disease for anti-TNF- α therapy.

- Identifying the appropriate patient for anti-TNF- α therapy
 - Who should receive anti-TNF- α agents?
 - Confirmation of active inflammatory bowel disease
 - Excluding Disease Mimickers
 - Exclude contraindications to biologic therapy
- Biologic pretherapy counseling
 - Discussion of costs and potential risks and benefits
 - Patient's information leaflets
- Screening for latent infections
 - Tuberculosis, hepatitis B and C, HIV
- Baseline laboratory tests
 - Full blood count, varicella zoster virus test (if prior infection by chicken pox or shingles is uncertain), urea, creatinine, electrolytes, liver function test, C-reactive protein and/or fecal calprotectin
- Assessment and update vaccination status

Table 2. Clinical factors associated with a complicated or disabling Crohn's disease course*.

- Age at diagnosis <40 years old
- Need for steroid use to treat the first flare
- Retal ou perianal disease
- Weight loss >5 kg
- Cigarette smoking
- Deep colonic ulcers on endoscopy
- Extensive small bowel disease

* Adapted from references [6,7].

a more aggressive top-down strategy (ie, therapy with anti-TNF- α agents in combination with azathioprine) early in the CD course may be the first-line therapy for patients presenting 2 or more predictive clinical factors of complicated disease behavior and of more rapid progression of CD (Table 2) [6,7]. In addition, anti-TNF- α therapy should be considered as first-line therapy in CD patients with bowel damage (stricture/fistula/abscess), and/or severe disease, and/or complex perianal fistulas [8], as well as for individuals with extensive severe ulcerative colitis (UC) not rapidly controlled by mesalazine and/or oral steroid treatment [9].

Confirmation of active inflammatory bowel disease

Accurate assessment of disease activity is essential prior to starting anti-TNF- α therapy for IBD patients in order to provide appropriate treatment. This evaluation must not be based only on present symptoms. The Crohn's Disease Activity Index, which is widely used in CD patients, has been proven quite inaccurate in this context (for instance, the score might be raised in the absence of inflammation because of diarrhea and pain due to irritable bowel syndrome or bacterial overgrowth) [10].

Table 3. Formal contraindications to anti-TNF- α therapy.

- Serious active infection
- Untreated latent tuberculosis
- Moderate-to-severe heart failure
- Known hypersensitivity to anti-TNF agents
- Multiple sclerosis or another neurological demyelinating disorder
- Optic neuritis
- Previous lymphoma or current malignancy
- Congenital or acquired immunodeficiency

Likewise, patients who have abdominal pain, nausea, vomiting, and even diarrhea may have fibrostenotic strictures and are not appropriate for anti-TNF- α therapy [11]. Therefore, depending on clinical setting, IBD-related inflammatory activity should be established by ileocolonoscopy and/or computed tomography or magnetic resonance enterography and/or fecal markers (e.g., calprotectin) and/or C-reactive protein.

Excluding disease mimickers

Prior to commencing anti-TNF- α therapy for patients with IBD, other illnesses with a similar presentation need to be excluded. Foremost among these is irritable bowel syndrome. A recent meta-analysis of patients with IBD demonstrated that 25–46% of those in clinical remission have symptoms compatible with a diagnosis of irritable bowel syndrome [10]. Patients who are in remission, but who experience important functional symptoms (e.g., abdominal pain, distension, and diarrhea) may have symptoms that mimic active disease, and thus receive inappropriate and potentially harmful anti-TNF- α therapy.

Bacterial gastroenteritis can simulate activity in IBD, and upon suspicion of acute gastroenteritis, the patient's feces should be cultured for pathogenic enteric bacteria [12]. Additionally, the risk of *Clostridium difficile* colitis is increased in patients with IBD, regardless of medication use, hospitalizations, or recent antibiotic exposure; thus, it is recommended the feces of all IBD patients with diarrhea be examined for cytotoxins A and B of *Clostridium difficile* [12]. In patients with severe IBD (mainly those who recently used immunosuppressive medications), ileocolonoscopy with biopsies should be performed to exclude superinfection by cytomegalovirus [13]. Other non-infectious conditions that can mimic IBD symptoms and that should be excluded include bile salt diarrhea (in patients with previous ileal resection), small-bowel bacterial overgrowth, drug-induced diarrhea, carbohydrate malabsorption, and colon cancer [14].

Exclude contraindications to biologic therapy

A thorough history should be obtained to assess for contraindications to anti-TNF- α therapy (Table 3). These include serious

Table 4. Considerations for prescribing immunosuppressant or anti-TNF- α agents in inflammatory bowel diseases patients with previous cancer*.

- Make sure that there is no other occult cancer before initiating immunosuppressants or anti-TNF- α therapy
- Try to respect a 2-to-5 years pause for cancers with intermediate to high risk of relapse (i.e. breast, uterine body, colon, prostate, urinary tract cancers, sarcoma, melanoma, myeloma and nonmelanoma skin cancers)
- Prefer monotherapies and step-up approach, initiating with methotrexate if appropriate
- Cooperate with oncologists

* Adapted from reference [18].

active infection, untreated latent tuberculosis, moderate-to-severe heart failure, a clear history of multiple sclerosis or optic neuritis, a known hypersensitivity to anti-TNF- α drugs, a present malignancy or history of lymphoma, and congenital or acquired immunodeficiency [15]. Furthermore, anti-TNF- α therapy should be used with caution in patients with mild heart failure as well as in those with a prior malignancy [16]. Initiating immunosuppressive therapy in a patient with previous cancer is a case-by-case and difficult decision because there are no consensus guidelines to assist in managing IBD patients in this clinical setting [17]. Nonetheless, some suggestion may be incorporated into clinical practice based on extrapolation from observational studies of patients with rheumatoid arthritis (RA) or solid-organ transplants (Table 4) [17,18].

Biologic Pretherapy Counseling

Once a decision has been taken about the appropriateness of anti-TNF- α therapy for an individual patient, it is important this treatment be discussed with the patient, putting into perspective the benefits, cost, and risks. Patient education can consist of either a face-to-face discussion or the recommendation of educational materials, including giving an informational leaflet about the drug [11]. One of the best ways to obtain reliable information is from professional organization such as CCFA and/or ECCO. Another resource is through reputable Internet sites (for example, <http://www.youandibd.com>). When clinically indicated, the benefits of anti-TNF- α agents usually outweigh the risks, but this should be assessed and discussed on a case-by-case basis with each patient [19]. A thorough explanation of the risks of this therapy, including rare but serious adverse effects such as opportunistic infections, including tuberculosis and lymphomas (particularly when in combination with thiopurines), must be outlined to patients prior to the beginning of therapy. Of note, in IBD patients using an immunosuppressant (especially thiopurines), increased risk of Epstein-Barr virus-related lymphomas, non-melanoma skin cancers, and uterine cervix abnormalities has been reported

Table 5. Proposed strategies for reducing the risk of immunosuppression-related lymphomas and cancers in inflammatory bowel diseases patients*.

- Work-up for clinically silent pre-existing neoplasm in patients older than 50 years with late-onset IBD, including screening for breast cancer in women and prostate cancer in men
- Protect against UV radiation (sunscreening) and receive annual dermatological screening
- Avoid combination therapy with thiopurines and anti-TNF- α in young males (<35 years) beyond a duration of 2 years, especially when IBD is on remission (> risk of hepatosplenic T- cell lymphoma)
- Avoid thiopurines on patients >65 years (> risk of lymphomas)
- Yearly screening for human papillomavirus via Pap smear testing, mainly on IBD women who are sexually active as well as to order human papillomavirus vaccination for IBD women between 9–26 years old, preferentially before the beginnings of any immunosuppressive therapy

* Adapted from references [17,18].

[18]. A mild increase in the risk of melanoma has been reported in patients treated with anti-TNF- α agents [20]. It is important to highlight that these risks are quite low, particularly if screening and prophylactic measures are employed. In addition, these risks must be placed in perspective with risks of not using anti-TNF- α therapy, particularly the potential for disease complications or progression [21]. For example, it is well known that the risk of poorly controlled CD and/or long-term steroid use is associated with higher rates of mortality when compared to patients receiving an immunosuppressant [22].

A series of preventive measures likely to attenuate the excess risk of cancers in IBD patients undergoing immunosuppressive therapy must be taken (Table 5). Patients should be advised that anti-TNF- α medications should be stopped if fever, persistent cough, skin rash, systemic symptoms or other unexplained symptoms develop, which could be infections signs [23]. Once the medication is stopped, it should not be restarted until the patient has discussed it with their doctor. Moreover, patients should know that smoking cigarettes might reduce the efficacy of anti-TNF- α agents, and therefore they should be encouraged to stop smoking and get help to do so if necessary before beginning therapy. Also essential is a discussion about maintaining therapy, because intermittent treatment or extended discontinuation of a biological may cause immune reactions if the anti-TNF- α is reinitiated [23].

Importantly, the clear communication between patients and their doctors must include an approach to the potential benefits of anti-TNF- α therapy for IBD. The potential for achieving optimal outcomes should be emphasized, such as resolution

and/or control of inflammation, attenuation of symptoms, prevention of relapse, improvement in quality of life, and reduced hospitalizations, surgeries, bowel damage, and disability [5–7]. Ultimately, proper education is pivotal, and the understanding of the risks and benefits of anti-TNF- α therapy by individuals depends mainly on the content of information and how it is communicated by the clinician [21].

Screening for Latent Infections

An increased risk of both opportunistic infections and latent infection flare-up is observed during anti-TNF- α therapy; thus, an efficient strategy must be used to try to reduce the occurrence of adverse events. If we consider that in such circumstances infections can have significant morbidity and potential fatal outcome, it is necessary to establish rules to be followed to identify latent and sometimes silent infections before the use of this class of drugs [12]. In particular, we discuss the screening for tuberculosis (TB), hepatitis B and C, varicella zoster virus (VZV), and human immunodeficiency virus (HIV).

Tuberculosis

Screening should be performed for detecting both active and latent TB infection (LTBI) in all patients considering biologic therapy because anti-TNF- α increases the risk of latent TB flare-up regardless of the type of anti-TNF- α considered [24]. Nearly 4-fold greater risk was noticed in Denmark and Sweden in 10 years of experience with this kind of treatment, although other non-notified cases may have occurred, resulting in incidence higher than the registered data [12,25]. Moreover, it has been observed that prophylactic therapy reduces the risk of TB reactivation and brings a significant decrease in TB cases with screening and preventive treatment before initiating anti-TNF- α [26]. In such circumstances it is currently recommended that patients must be screened for latent TB, and appropriate therapy (isoniazid) must be initiated 1 month before, in all patients who need biological use for IBD treatment [12].

Unfortunately, there is no absolute specific and sensitive test for detection of LTBI, and so it is impossible to recognize all the patients who will be at risk of developing active TB during the course of anti-TNF- α therapy. People who lived in close contact with individuals with active TB or in areas of high incidence of disease for more than 3 months, those with chest X-ray with signs of previous infectious TB, or who have been treated for active TB or LTBI in the past are at higher risk of developing active TB during anti-TNF- α treatment. The diagnosis of LTBI through Mantoux or tuberculin skin test (TST) has been used for several years to identify LTBI. It is currently suggested to replace the TST with an interferon gamma release assay (IGRA)

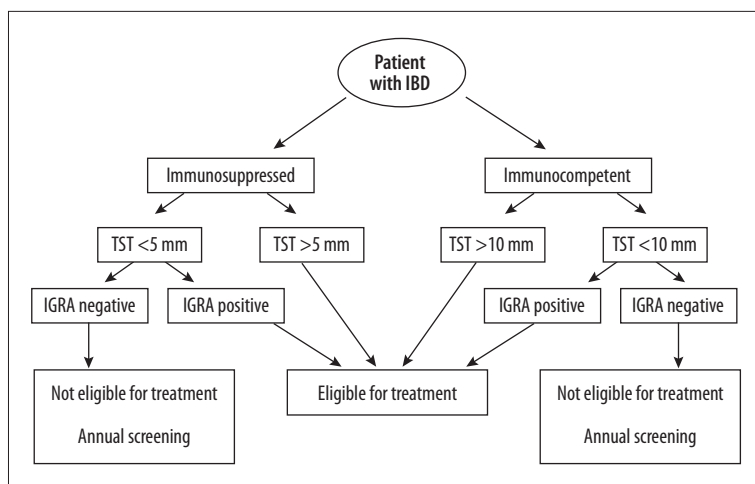


Figure 1. Algorithm for treatment of latent tuberculosis infection in IBD patients – Adapted from Duarte et al. [29].
 * IBD – inflammatory bowel disease;
 TST – tuberculin skin test;
 IGRA – interferon- γ release assay.

tested in a blood sample to identify people who are infected with *Mycobacterium tuberculosis* (MTB). IGRA is more specific and sensitive, having no false-positive results and thus reducing the risk of false-negative results in immunosuppressed patients with anergic reaction to TST. Indeed, it is important to acknowledge the low sensitivity of the TST for detecting latent TB in patients using corticosteroids at doses greater than 20 mg for longer than 2 weeks, who are taking effective doses of immunomodulators, or with significant protein-calorie malnutrition, which is likely to include the majority of individuals beginning anti-TNF- α therapy [26]. In these settings the IGRA may be much more worthwhile than the TST, although neither test is able to distinguish between active and latent TB [27]. However, the IGRA test is not yet available in every country and TST is still the most frequently used and most available test in poorer countries due to its cheapness. The IGRA test should be given in combination with a chest X-ray and patients should be submitted to both before starting anti-TNF- α therapy. The assessment of risk factors associated to a chest X-ray and an IGRA, or a TST when IGRA cannot be performed, may be the more appropriate screening strategy for all patients to identify LTBI. The concomitant use of 2 or more immunosuppressive drugs such as prednisone, azathioprine /6-mercaptopurine, methotrexate, or anti-TNF- α may lead to inconclusive or false-negative results of IGRA as well as TST. Some authors suggest the use of both IGRA and TST to increase the chance of identifying LTBI in immunosuppressed patients before adding anti-TNF- α to the treatment [28,29]. Cotter and Rosa [28] reported an interesting approach to choose the eligibility for treatment of LTBI, based on a very practical algorithm adapted from Duarte et al. [29] to trace the routes to be followed to decide which patients will need tuberculosis treatment according to IGRA and TST (Figure 1). They also emphasize that if chest X-ray results suggest previous untreated tuberculosis, patients should be eligible for treatment after exclusions of active tuberculosis, regardless of the IGRA or TST test results. Patients may start biological therapy after 1–2 months of a

total of 9 months of anti-tuberculosis treatment [30]. If conditions for performing the IGRA test do not exist, TST associated with chest X-ray can be used, in addition to considering the clinical history and physical examination. A TST of ≥ 5 mm in patients who have HIV, a recent TB contact, a chest X-ray consistent with prior TB, organ transplants, and those receiving corticosteroids or other immunosuppressives indicate that they are at high risk of having LTBI and should be treated for 9 months. However, most patients cannot wait that long and need to start therapy sooner after 1–2 months of isoniazid. However, some circumstances impose the urgent use of anti-TNF- α , which can avoid, for instance, a surgical procedure. In cases of uncertainty about whether there is a medical history or radiological suspicion of LTBI, TB prophylaxis must be initiated, and the patient should be referred to a pulmonary specialist.

All patients must be regularly assessed for signs of reactivation because tests for screening are not 100% sensitive and cannot predict with complete safety which patients will develop active TB during anti-TNF- α therapy [12]. Therefore, the ideal screening schedule is to submit all patients to TST, IGRA, and chest X-ray before treatment with anti-TNF- α , because there is also a high prevalence of anergy in IBD patients. If the IGRA test cannot be used, all patients must be submitted to a TST and a chest X-ray to investigate active or latent TB. In cases in which a TST has < 5 mm of induration and chest X-ray result is normal, anti-TNF- α therapy can be started without other procedures. However, if chest radiography results are abnormal, 3 sputum samples must be examined for TB [31]. If results are negative, the treatment with INH for LTBI must be started for 9 months, delaying biological therapy for at least 4 weeks. If positive, complete treatment for active TB must be initiated for 6–12 months, deferring anti-TNF- α as long as possible until the end of TB treatment. If TST has > 5 mm of induration, sputum samples are negative for MTB, and chest radiograph is normal, treatment for LTBI should be initiated, but if chest X-ray is abnormal, the treatment of active TB must be

started, independent of sputum investigation being positive or negative. If the chest X-ray shows images consistent with residual TB, the patient should be referred to a pulmonary specialist [30]. Patients who develop active tuberculosis during anti-TNF- α treatment should receive full anti-mycobacterial chemotherapy, but may continue with their anti-TNF therapy if clinically indicated [16].

Hepatitis B and C

Hepatitis B

Hepatitis B virus (HBV) has infected one-third of the world's population and can be prevented by vaccination [32]. Although it has been reported that patients with IBD have an increased risk of acquiring viral hepatitis [33], recent studies demonstrated that the prevalence of HBV in IBD patients does not differ of that found in the general population [34,35]. Taking into account that patients with IBD may need immunosuppressive drugs at some point during treatment, it is necessary to screen all patients for HBV markers at diagnosis, since that it is well known that patients receiving immunosuppressants, including anti-TNF- α agents, may have reactivation of HBV as well as hepatic decompensation [36]. Serologic assessment for HBV must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) with levels, and hepatitis B core antibody (HBcAb). It is imperative to vaccinate patients who lack serum protector level of anti-HBs (≥ 10 U) before anti-TNF- α therapy, because an increasing number of hepatitis B reactivation has been reported when no preventive measure is adopted. A full vaccination course (0, 1, and 6 months) for HBV is recommended in patients that have not received vaccine previously, and a booster dose must be used in those vaccinated when anti-HBs level is below 10 units [37]. If active HBV is found, prophylactic therapy with an anti-nucleotide should be started at least 1–3 weeks before biological employment, and anti-TNF- α therapy should be delayed until a negative HBV DNA viral load is obtained, which may require 2–3 months [37,38]. In this situation, antiviral therapy should be maintained for at least 6 months after biologic therapy withdrawal [37]. Additionally, IBD patients who are positive for the hepatitis B surface antigen, with or without active viral replication, should receive antiviral prophylaxis before undergoing immunosuppression in order to avoid HBV reactivation [38]. Prophylaxis should be ordered regardless of the number and type of immunosuppressants used, whether steroids, immunomodulators, or biologics [38]. Tenofovir/entecavir is preferred over lamivudine as nucleoside analogues due to their better resistance profile.

Although less common, HBV reactivation can also occur during immunosuppressive therapy in patients with occult HBV

infection defined by a quiescent infection in HBsAg/anti-HBc-positive or anti-HBc-positive/anti-HBs-positive patients and DNA persisting in the nucleus of hepatocytes [39]. IBD patients with occult HBV should be monitored for alanine aminotransferase and HBV DNA during throughout their treatment with immunosuppressant [37,40].

If anti-TNF- α therapy is used in HBV-infected patients who also receive concomitant anti-viral treatment, the outcome from case reports has been good for infliximab and adalimumab, with no evidence of viral reactivation. Serum aminotransferases remained normal and there was no increase in viral load during treatment with each of the 3 anti-TNF- α agents. Liver dysfunction in patients with IBD treated with an immunosuppressant is more frequent and severe in those with HBV than in HCV carriers and is associated mainly with combined immunosuppression [37,38].

Hepatitis C

Concurrent hepatitis C virus (HCV) infection in IBD patients is uncommon. Treatment of IBD with infliximab in HCV patients did not result in flares in hepatic biochemical tests, and there was improvement in the IBD disease activity score [41]. The role of anti-TNF- α in hepatitis C virus (HCV) replication is not well understood but it is assumed that IBD patients with HCV can be treated with anti-TNF- α and the screen for HCV would be unnecessary [12]. However, as far as we are concerned, it seems prudent to identify patients with HCV and IBD before anti-TNF- α therapy and to evaluate the degree of hepatic injury that is present, because patients with advanced fibrosis or even cirrhosis may be more predisposed to infections by the liver disease in itself, and the use of biological drugs may require more caution regarding the doses and the interval between them. This aspect of IBD and HCV is not yet completely clarified. Treatment of hepatitis C in patients with IBD was recently indicated as effective and safe with interferon and ribavirin, the same as in patients without IBD [42]. However, the safety profile of anti-TNF- α agents in the setting of HCV infection seems to be acceptable, even if differences in the hepatotoxic profile are apparent between different agents, and, in the absence of long-term and large controlled clinical trials, a definitive statement on the safety of anti-TNF- α therapies in the setting of chronic HCV infection cannot be made [41].

Human Immunodeficiency Virus

In HIV patients, tumor necrosis factor increases the viral replication; administration of anti-TNF- α was considered as an interesting way to try to reduce the viral load and lessen the effects of HIV disease. However, it was tried for HIV patients, without any benefits. There are some case reports of treatment

of HIV patients with anti-TNF- α , and all the patients who were submitted to therapy had a satisfactory CD4 cells count, no co-infection, and low HIV viral load [43]. We conclude that in HIV patients with IBD who have immunodeficiency under control and who need anti-TNF- α treatment, the drug can be used in a multidisciplinary approach during therapy [44].

Assessment and Update Vaccination Status

In an attempt to control the state of chronic inflammation of the intestinal and systemic mucosa with the use of immunosuppressive and immunomodulatory therapy in the treatment of IBD, the desired effects can result in increased susceptibility to infections [45–47]. Fulminating and fatal infections have already been described in IBD patients treated with drugs such as corticosteroids, azathioprine, 6-mercaptopurine, and biologics. Some of them can be prevented by vaccination and immunization strategies [45,48,49].

The effectiveness of vaccination in this group of patients depends on the quality of the immune system, which must present with quantitatively normal levels of IgG, IgA, IgM, and IgE, similar to the general population, with preserved humoral and cellular immunity. What actually occurs is an exaggerated response to various external stimuli, demonstrating one aspect of IBD pathogenesis. Therefore, an adequate response after vaccination in patients with CD and UC, in the absence of immunomodulatory therapy, is expected [50–52]. Bearing this fact in mind, a few strategies have been created to safely guide the management of IBD patients using immunosuppressive therapy [52,54].

The best initial approach should be taken during the first contact with treatment-naïve patients with suspected CD or UC [50–52,54]. Risks of exposure, such as occupation, housing, and travel to endemic areas, should be verified as well as the updated vaccination card, following the general recommendations according to the immunization schedule recommended by the Ministry of Health. It should be emphasized that vaccination in these patients is not associated with reactivation of IBD [52,54]. However, care must be taken prior to vaccine administration in those patients using immunosuppressive therapy since no vaccines with live agents can be used due to the risk of spread [51–54]. When possible, evaluation of antibodies to some infectious diseases (e.g., chickenpox) might be performed to determine if specific vaccines are required [52,54].

Live Attenuated Vaccines

Live attenuated vaccines such as measles, mumps, rubella, polio (Sabin), yellow fever, varicella, BCG, oral typhoid, and inhaled

influenza (intranasal) should not be administered to immunosuppressed patients, including those on current treatment or who recently (within the last 3 months) received prednisone 20 mg/day or equivalent for 2 weeks or more, azathioprine, 6-mercaptopurine or methotrexate, anti-TNF therapies, or to those with severe malnutrition [50]. If vaccination is required in cases of mumps and rubella, wait 6 weeks to start treatment with immunosuppressants. With those wishing to travel to areas where yellow fever is endemic, institute therapy 1–3 months after vaccination and in other cases wait at least 1 month after vaccination [51].

It is important to assess on IBD patients the varicella immune status at diagnosis and prior to starting any immunosuppressive therapy. In patients without a history of varicella, herpes zoster, or varicella vaccination, it is necessary to assess serum antibody titers [50–52,54]. The ECCO guidelines recommend immunization with varicella-zoster virus (VZV) vaccine at least 3 weeks before onset of immunomodulator therapy, and preferably at diagnosis of IBD, if the medical history of chickenpox, shingles, or VZV vaccination is negative [55]. Although patients using short-term corticosteroid therapy (≤ 2 weeks), low doses of methotrexate, azathioprine, or 6-mercaptopurine have safely received zoster vaccine, most experts are cautious in ordering them due to the theoretical risk of disseminated illness [56].

Although not specific for IBD, the recent guidelines of the Infectious Diseases Society of America (IDSA) [54] may be a good guide. In sum, the IDSA guideline recommends that zoster vaccine:

- Should be given to patients aged ≥ 60 years if it can be administered ≥ 4 weeks before beginning highly immunosuppressive therapy;
- Should be considered for varicella-positive patients (persons with a history of varicella or zoster infection or who are VZV seropositive with no previous doses of varicella vaccine) aged 50–59 years if it can be administered ≥ 4 weeks before beginning immunosuppressive therapy;
- Should be administered to patients aged ≥ 60 years who are receiving therapy considered to induce a low level of immunosuppression (Table 6);
- Should not be administered to highly immunocompromised patients (Table 6).

Inactivated Vaccines

Inactivated vaccines are well tolerated by immunosuppressed patients, but there may be an inability to confirm seroconversion and maintain antibody titers at protective levels [52]. Pneumococcal and influenza (injectable), the 2 most common infections in adults with high morbid-mortality in patients over 65 years old, can be prevented with vaccination [50–52,54].

Table 6. Definitions of high- and low-level immunosuppression according to the Infectious Diseases Society of America [54].

<p>Patients with high-level immunosuppression include those</p> <ul style="list-style-type: none"> • With combined primary immunodeficiency disorders (i.e., severe combined immunodeficiency) • Receiving cancer chemotherapy • Within 2 months after solid organ transplantation • With HIV infection with a CD4 T-lymphocyte count <200 cells/mm³ for adults and adolescents and percentage <15 for infants and children • Receiving daily corticosteroid therapy with a dose \geq20 mg (or >2 mg/kg/day for patients who weigh <10 kg) of prednisone or equivalent for \geq14 days • Receiving certain biologic immune modulators, that is, a tumor necrosis factor-alpha (TNF-α) blocker or rituximab
<p>Patients with low-level immunosuppression include</p> <ul style="list-style-type: none"> • Asymptomatic HIV-infected patients with CD4 T-lymphocyte counts of 200-499 cells/mm³ for adults and adolescents and percentage 15–24 for infants and children • Those receiving a lower daily dose of systemic corticosteroid than for high-level immunosuppression for \geq14 days or receiving alternate-day corticosteroid therapy • Those receiving methotrexate (MTX) \leq0.4 mg/kg/week, azathioprine \leq3.0 mg/kg/day, or 6-mercaptopurine \leq1.5 mg/kg/day

The group of vaccines with dead or inactivated virus also includes rabies, injectable typhoid, hepatitis A and B, HPV (human papilloma virus), meningococcal and tetanus, and diphtheria for adults [52].

All individuals with IBD should receive the inactivated vaccine against influenza on an annual basis regardless of patient immune status [55]. The intranasal influenza vaccine is contraindicated in immunosuppressed individuals. In addition, at least 1 dose of pneumococcal vaccine should be administered, with revaccination after 5 years, to patients who are over 65 years and/or immunosuppressed [50–52]. Tetanus and diphtheria vaccines should be administered every 10 years, and at least once in a lifetime it should be associated with pertussis. The meningococcal vaccine may be given to IBD patients, especially those at risk for this infection, as in patients with splenectomy [50–52].

The hepatitis B vaccine response can be reduced, and when anti-HBsAg titers are undetectable or are lower than 10 mU/mL, a new scheme must take place with the doubling of each of the 3 doses (40 μ g) or a booster dose at the 12th month. If there is urgency to start the immunosuppressive therapy, shortening the vaccine scheme is allowed (0, 1, and 2 months instead of the conventional regimen of 0, 1, and 6 months) [53]. In cases of hepatitis A, if no circulating antibodies are observed, the indication is 2 doses and a booster after 10 years [52,54].

HPV vaccine is recommended for women 9–26 years old before or beginning sexual activity, as well as for patients with a history of condyloma, HPV infection (positive DNA test), or with abnormal Pap smear results. Women with IBD with or without the use of immunosuppressants, regardless of sexual activity, should also be vaccinated because they are considered high-risk. To date, there is no evidence that cervix cancer is increased in this group of patients, but the risk should

not be ignored [50–52,54]. General vaccination strategies are listed in Table 7.

Vaccination of Newborns

It is important to remember to vaccinate newborns whose mothers used infliximab in the last quarter of pregnancy. The presence of circulating drug in newborns up to 6 months postpartum has been reported; therefore, vaccines for rotavirus and BCG should not be administered. The same rationale should be applied to other biologics, although there have been no studies about this topic to date. All vaccines with dead or inactivated viruses can be administered [51,52,54,57].

Biologics and Fertility, Conception, and Pregnancy

IBD is a condition that can affect both women and men during their reproductive years [58]. Several studies reported higher incidence rates of adverse pregnancy outcomes in women with IBD [59,60]. Therefore, understanding the nuances of IBD management in women who are considering pregnancy, attempting to conceive, or who are already pregnant, is an important task for physicians who treat IBD, which mainly affects young people who are fertile and of reproductive age. This issue must be considered in both sexes, although women deserve more attention because the disease, as well as the drugs employed in its treatment, may have direct consequences for the mother and the child. Considering the biologic safety, infliximab has the most robust data registered at present. This is because it has been evaluated in many more trials than any other biologic agent. In addition, post-marketing experience provides very valuable information about adverse events occurring during treatment with this agent [61]. Regardless, there remains a concern regarding

Table 7. Vaccination strategies in inflammatory bowel disease patients

General measures	Check vaccination card and complement it if necessary
	Check immune status
At diagnosis	Hepatitis A and B
	Pneumococcal
	Influenza
	HPV
Yearly	Influenza
Every 5 years	Pneumococcal
Every 10 years	Tetanus and diphtheria (for adults)
Risk situations	Meningococcal
Contraindicated in the presence of immunosuppression: Vaccinate 3 months before immunosuppression or 3 months after stopping immunosuppression	Herpes zoster or varicella
	Yellow fever
	Rabies
	Triple viral vaccine
	BCG
	Polio – Sabin
When traveling	Evaluate 3 months before traveling
	Consult with an infectologist on the place to be visited
	Hepatitis B vaccine booster
Possible substitutes in case of high risk	Inactivated polio vaccine
	Hemophilus
	Immunoglobulin for hepatitis B, rabies, tetanus and herpes zoster

* Adapted from Rahier [57].

safety of anti-TNF- α therapy during conception, pregnancy, and breastfeeding. Overall, data on the safety of anti-TNF therapy are largely derived from uncontrolled case reports or case series. Growing evidence suggests that exposure to anti-TNF drugs at the time of conception or during pregnancy does not result in an increased risk of adverse pregnancy outcomes or congenital malformations [61]. For example, Bortlik et al. [62] studied children exposed to anti-TNFs drugs prenatally for maternal IBD in 3 centers in the Czech Republic and postnatal development of children exposed to anti-TNF- α during pregnancy was also evaluated. They concluded that prenatal exposure to anti-TNF- α antibodies seems to be safe for fetal development. Data on long-term outcome of exposed children are lacking [61,62]. Schnitzler et al. [63] assessed pregnancy outcomes in 212 women with IBD under anti-TNF- α therapy and reported that direct exposure to biologics during pregnancy was not related to a higher incidence of adverse pregnancy outcomes than IBD overall.

Another relevant aspect involves the consequences of anti-TNF- α agent exposure to conditions of fertility and conception in patients with IBD. Active CD, especially at the time of conception, might be associated with a higher risk of premature delivery, often combined with low birth weight (LBW), spontaneous abortion, stillbirth, and neonatal defects [63]. However, a recent case-control study found that women with either CD or UC have a similar pregnancy outcome when compared with a population of non-IBD pregnant women [64]. Moreover, active disease at the time of conception seems to be the main factor predisposing to adverse pregnancy outcomes, and physicians often recommend their patients with active disease to avoid pregnancy, although IBD patients may actively desire pregnancy. Improved IBD therapy lets more women consider pregnancy and allows treating physicians to support pregnancy in women with IBD, but concerns regarding the use of drugs during conception, pregnancy, and lactation are often raised

by IBD patients [63]. We consider that the matter should be discussed with the patient at the time of starting IBD therapy and that the physician should discuss all the risks and benefits of therapy and of disease activity in order to allow the patient to understand and participate in the final decision and decide when it would be best to become pregnant. Curiously, increased TNF- α has been associated with infertility and TNF- α blockade is being investigated as a potential therapy for this condition. The idea that anti-TNF- α agents might be useful in patients who have trouble becoming pregnant came from basic science studies showing that these drugs could have pro-reproductive effects, and a hypothesis was generated that TNF- α blockers should work in the subset of women with reproductive failure who have high Th1/Th2 cytokine ratios [65]. Thus, hypothetically, anti-TNF- α use may increase the chance of becoming pregnant in patients with IBD.

While initial concerns focus on attaining a durable remission and avoiding the adverse effects of medications, once in remission, the focus often shifts to the effect of disease and the medications used to treat it on fertility and the ability to give birth to a healthy child [66]. Mañosa et al. [67] assessed the impact of IBD and its treatment on fertility, pregnancy outcomes, and breastfeeding through a questionnaire posted to 850 adults with IBD. They conclude that the infertility rate among IBD patients seems to be similar to that seen in the general population.

The influence of anti-TNF- α therapy on male fertility was described 4 years before by Saougou et al. [68] in patients with spondyloarthropathies, concluding that there was some supportive evidence for the safe use of infliximab in male patients who have inflammatory diseases during their peak reproductive years.

Another very relevant point is that the safety of medical therapy during pregnancy and lactation is a major concern for both pregnant women and their partners as well as for physicians. As a general rule, the benefit of continuing medical therapy in IBD, including biological therapy during pregnancy, outweighs the potential risks in the vast majority of instances [69], and physicians must let patients know that anti-TNF- α agents can offer a chance of IBD remission and decreases risks to pregnant women when it occurs with uncontrolled disease activity.

References:

1. Feagan BG, Panaccione R, Sandborn WJ et al: Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology*, 2008; 135: 1493–99
2. de Souza GS, Vidigal FM, Chebli LA et al: Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients. *Med Sci Monit*, 2013; 19: 716–22
3. Peyrin-Biroulet L, Oussalah A, Williet N et al: Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut*, 2011; 60: 930–36
4. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology: Management of Crohn's disease in adults. *Am J Gastroenterol*, 2009; 104: 465–83

It must be stressed that monoclonal antibodies can cross the placenta, mainly during the third trimester, although they seem to be safe, at least in the short-term [61,70]. However, live vaccines should be avoided in children with in utero exposure to biologics for at least the first 6 months of life. Although biologics have been detected in breast milk in small amounts, the extent to which they are absorbed by the infant is unclear [61,70]. At present, it seems that the possible deleterious effect of this exposure on the neonate is unlikely but cannot be ignored [61].

An increase in infections risk has been reported in infants exposed to combination therapy with thiopurines and anti-TNF agents in utero [71]. Therefore, it has been proposed that anti-TNF therapy should be withdrawn during the second trimester [58,61]. On the other hand, pegol certolizumab is a pegylated humanized antibody Fab fragment against TNF, and as such lacks an Fc receptor; therefore, it may not be necessary to discontinue it during pregnancy [70,72].

Conclusions

Appropriate patient selection, counseling, and education are all important issues for the successful use of the anti-TNF- α therapy in IBD patients. Accurate assessment of disease activity is essential prior to starting biologics in order to provide appropriate treatment. Also it is important to exclude disease mimickers such as irritable bowel syndrome and *Clostridium difficile* superinfection. A careful history should be obtained to assess contraindications to anti-TNF- α therapy. Preceding anti-TNF- α therapy, the patients need to be screened for latent tuberculosis, hepatitis B virus infection, and (usually) hepatitis C virus and HIV infection. Screening and vaccination in IBD patients have now become part of the new standard of care. At the time of IBD diagnosis, a vaccination history should be taken, and any “catch-up” vaccinations should be administered. Patients with IBD should receive all regularly scheduled vaccines, except for patients receiving immunosuppressive therapies, who should not receive live vaccines. In addition, patients who receive live virus vaccines should not receive biologic therapy for 3 months. Ultimately, the benefits of anti-TNF- α agents usually outweigh the risks, but this should be assessed and discussed on a case-by-case basis with each patient.

5. Peyrin-Biroulet L, Fiorino G, Buisson A, Danese S: First-line therapy in adult Crohn's disease: who should receive anti-TNF agents? *Nat Rev Gastroenterol Hepatol*, 2013; 10: 345–51
6. Vermeire S, Ferrante M, Rutgeerts P: Recent advances: personalised use of current Crohn's disease therapeutic options. *Gut*, 2013; 62: 1511–15
7. Bouguen G, Levesque BG, Feagan BG et al: Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease. *Clin Gastroenterol Hepatol*, 2013; pii: S1542-3565(13)01301-3
8. Allen PB, Peyrin-Biroulet L: Moving towards disease modification in inflammatory bowel disease therapy. *Curr Opin Gastroenterol*, 2013; 29: 397–404
9. Louis E: Strategic use of immunosuppressants and anti-TNF in inflammatory bowel disease. *Dig Dis*, 2013; 31: 207–12
10. Halpin SJ, Ford AC: Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*, 2012; 107: 1474–82
11. Kane SV: Preparing for biologic or immunosuppressant therapy. *Gastroenterol Hepatol*, 2011; 7: 544–46
12. Nordgaard-Lassen I, Dahlerup JF, Belard E et al: Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment. *Dan Med J*, 2012; 59: C4480
13. Dignass A, Lindsay JO, Sturm A et al: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis*, 2012; 6: 991–1030
14. Buchner AM, Blonski W, Lichtenstein GR: Update on the management of Crohn's disease. *Curr Gastroenterol Rep*, 2011; 13: 465–74
15. Van Assche G, Lewis JD, Lichtenstein GR et al: The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. *Am J Gastroenterol*, 2011; 106: 1594–602
16. Ding T, Ledingham J, Luqmani R et al: Standards, Audit and Guidelines Working Group of BSR Clinical Affairs Committee; BHRP. BSR and BHRP rheumatoid arthritis guidelines on safety of anti-TNF therapies. *Rheumatology*, 2010; 49: 2217–19
17. Bernheim O, Colombel JF, Ullman TA et al: The management of immunosuppression in patients with inflammatory bowel disease and cancer. *Gut*, 2013; 62: 1523–28
18. Beaugerie L: Use of immunosuppressants and biologicals in patients with previous cancer. *Dig Dis*, 2013; 31: 254–59
19. Siegel CA: Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. *Gut*, 2012; 61: 459–65
20. Raaschou P, Simard JF, Holmqvist M, Askling J; ARTIS Study Group: Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. *BMJ*, 2013; 346: f1939
21. Siegel CA: Review article: explaining risks of inflammatory bowel disease therapy to patients. *Aliment Pharmacol Ther*, 2011; 33: 23–32
22. Lewis JD, Gelfand JM, Troxel AB et al: Immunosuppressant medications and mortality in inflammatory bowel disease. *Am J Gastroenterol*, 2008; 103: 1428–35
23. Kane S: Preparing the patient for immunosuppressive therapy. *Curr Gastroenterol Rep*, 2010; 12: 502–6
24. Wallis RS: Infectious complications of tumor necrosis factor blockade. *Curr Opin Infect Dis*, 2009; 22: 403–9
25. Askling J, Forde CM, Brandt L et al: Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum*, 2005; 52: 1986–92
26. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V et al: Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum*, 2005; 52: 1766–72
27. Diel R, Lodenkemper R, Nienhaus A: Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a meta-analysis. *Chest*, 2010; 137: 952–68
28. Cotter J, Rosa B: The importance of IGRAs in patients candidates for biological therapy. *J Crohns Colitis*, 2013; 7: 928–29
29. Duarte R, Campainha S, Cotter J et al: Portuguese Society of Pulmonology; Portuguese Society of Gastroenterology; Portuguese Society of Dermatology and Venereology; Portuguese Society of Rheumatology. Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases candidates for biological therapy. *Acta Reumatol Port*, 2012; 37: 253–59
30. Theis VS, Rhodes JM: Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*, 2008; 27: 19–30
31. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement: *Am J Respir Crit Care Med*, 2000; 161(4 Pt 2): S221–47
32. Dusheiko G: Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. *Liver Int*, 2013; 33: 137–50
33. Biancone L, Pavia M, Del Vecchio Blanco G et al: Hepatitis B and C virus infection in Crohn's disease. *Inflamm Bowel Dis*, 2001; 7: 287–94
34. Loras C, Saro C, Gonzalez-Huix F et al: Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol*, 2009; 104: 57–63
35. Lok A, McMahon BJ: Chronic hepatitis. *Hepatology*, 2007; 45: 507–39
36. Rahier JF, Ben-Horin S, Chowers Y et al: European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*, 2009; 3: 47–91
37. López-Serrano P, Pérez-Calle JL, Sánchez-Tembleque MD: Hepatitis B and inflammatory bowel disease: role of antiviral prophylaxis. *World J Gastroenterol*, 2013; 19: 1342–48
38. Gisbert JP, Chaparro M, Esteve M: Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*, 2011; 33: 619–33
39. Raimondo G, Allain JP, Brunetto MR et al: Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol*, 2008; 49: 652–57
40. Shouval D, Shibolet O: Immunosuppression and HBV reactivation. *Semin Liver Dis*, 2013; 33: 167–77
41. Allen AM, Kim WR, Larson J, Loftus EV Jr: Efficacy and safety of treatment of hepatitis C in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*, 2013; 11: 1655–60
42. Brunasso AM, Puntoni M, Gulia A, Massone C: Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology*, 2011; 50: 1700–11
43. Cepeda EJ, Williams FM, Ishimori ML et al: The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis*, 2008; 67: 710–12
44. Walsh AJ, Weltman M, Burger D et al: Implementing guidelines on the prevention of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*, 2013; 7: e449–56
45. Melmed GY, Ippoliti AF, Papadakis KA et al: Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol*, 2006; 101: 1834–40
46. Vermeire S, Van Assche G, Rutgeerts P: Vaccination and infection prevention in inflammatory bowel disease. *F1000 Medicine Reports*, 2010; 2: 80
47. Wasan SK, Baker SE, Skolnik PR, Farraye FA: A practical guide to vaccinating the inflammatory bowel disease patient. *Am J Gastroenterol*, 2010; 105: 1231–38
48. Carrera E, Manzano R, Garrido E: Efficacy of the vaccination in inflammatory bowel disease. *World J Gastroenterol*, 2013; 19: 1349–53
49. Gisbert JP, Chaparro M: Vaccination strategies in patients with IBD. *Nat Rev Gastroenterol Hepatol*, 2013; 10: 277–85
50. Sands BE, Cuffari C, Katz J et al: Guidelines for immunizations in patients with inflammatory bowel disease. *Inflamm Bowel Dis*, 2004; 10: 677–92
51. Melmed GY: Vaccination strategies for patients with inflammatory bowel disease on immunomodulators and biologics. *Inflamm Bowel Dis*, 2009; 15: 1410–16
52. Sanchez-Tembleque MD, Corella C, Pérez-Calle JL: Vaccines and recommendations for their use in inflammatory bowel disease. *World J Gastroenterol*, 2013; 19: 1354–58

53. Shouval D: Hepatitis B vaccines. *J Hepatol*, 2003; 39(Suppl.1): S70–76
54. Rubin LG, Levin MJ, Ljungman P et al: 2013 IDSA Clinical Practice Guideline for vaccination of the immunocompromised host. *Clin Infect Dis*, 2014; 58(3): e44–100
55. Rahier JF, Ben-Horin S, Chowers Y et al: European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*, 2009; 3: 47–91
56. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC): Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*, 2008; 57(RR-5): 1–30
57. Rahier JF: Prevention and management of infectious complications in IBD. *Dig Dis*, 2012; 30: 408–14
58. Ng SW, Mahadevan U: Management of inflammatory bowel disease in pregnancy. *Expert Rev Clin Immunol*, 2013; 9: 161–73
59. Cornish JA, Tan E, Teare J et al: A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut*, 2007; 56: 830–37
60. Kornfeld D, Cnattingius S, Ekbohm A: Pregnancy outcomes in women with inflammatory bowel disease – a population-based cohort study. *Am J Obstet Gynecol*, 1997; 177: 942–46
61. Gisbert JP, Chaparro M: Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol*, 2013; 108: 1426–38
62. Bortlik M, Duricova D, Machkova N et al: Impact of Anti-Tumor Necrosis Factor Alpha Antibodies Administered to Pregnant Women With Inflammatory Bowel Disease on Long-term Outcome of Exposed Children. *Inflamm Bowel Dis*, 2014 [Epub ahead of print]
63. Schnitzler F, Fidder H, Ferrante M et al: Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis*, 2011; 17: 1846–54
64. Bortoli A, Pedersen N, Duricova D et al: Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003–2006. *Aliment Pharmacol Ther*, 2011; 34: 724–34
65. Clark DA: Should anti-TNF-alpha therapy be offered to patients with infertility and recurrent spontaneous abortion? *Am J Reprod Immunol*, 2009; 61: 107–12
66. Mahadevan U: Fertility and pregnancy in the patient with inflammatory bowel disease. *Gut*, 2006; 55: 1198–206
67. Mañosa M, Navarro-Llavat M, Marín L et al: Fecundity, pregnancy outcomes, and breastfeeding in patients with inflammatory bowel disease: a large cohort survey. *Scand J Gastroenterol*, 2013; 48: 427–32
68. Saougou I, Markatseli TE, Papagoras C et al: Fertility in male patients with seronegative spondyloarthropathies treated with infliximab. *Joint Bone Spine*, 2013; 80: 34–37
69. Biedermann L, Rogler G, Vavricka SR et al: Pregnancy and breastfeeding in inflammatory bowel disease. *Digestion*, 2012; 86(Suppl.1): 45–54
70. Hyrich KL, Verstappen SM: Biologic therapies and pregnancy: the story so far. *Rheumatology*, 2013 [Epub ahead of print]
71. Mahadevan U, Martin CF, Sandler RS et al: PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. *Gastroenterology*, 2012; 142(Suppl.1): S149
72. Mahadevan U, Wolf DC, Dubinsky M et al: Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*, 2013; 11: 286–92