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REVIEW ARTICLE

Review of the safety with biologics in inflammatory bowel disease

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Abstract

Biologics have completely changed the treatment (and life) of patients with inflammatory bowel disease (IBD). After the first ones, anti-tumor necrosis factor (TNF) biologics, two new biologics, with other therapeutic targets, are now in routine use in our patients, and some others are in different stages of research. They share many aspects, but differ in others, so their efficacy and safety may be different. Having predictors of efficacy and safety in a particular patient are one of the greatest challenges in IBD therapy, but we are far from achieving it. In any case, safety is key, especially in drugs used as maintenance therapy in a chronic disease such as IBD. Although biologics are generally safe when are used correctly, it is essential to be aware of their potential adverse events and their particularities in different situations. To minimize them, it is essential to use them in the ideal patient, to choose the right biologic at the right time, to carry out a series of prior measures before start them, and, finally, to monitor the treatment correctly. We will discuss the differences between biologics, essentially anti-TNF versus ustekinumab versus vedolizumab, in terms of adverse events as well as their particularities of use. Having the knowledge of their contraindications, use in special populations, the steps before start, and how to monitoring them is essential. Although sometimes there are alternatives to biologics such as "the new small molecules," they are not the purpose of this review.

Keywords: *Inflammatory bowel disease. Biologic. Safety. Side effects.*

Introduction

Biologics are defined as "a medicinal product or vaccine that has been produced by living organisms". The biologics we currently use in the treatment of inflammatory bowel disease (IBD) are large molecular proteins directed against specific targets. In contrast, the treatments that we often refer to as "conventional treatments" (non-biologics), are usually synthesized in the laboratory, have a simpler chemical structure and smaller molecular size. Due to these, biological therapies share some characteristics in their pharmacokinetics and pharmacodynamics, although they may present important differences between them in efficacy and safety.

Biologics have undoubtedly improved the treatment of IBD and we are using them more and more frequently. In acute treatment, safety is important, but it becomes a key factor in their long-term use, which is necessary in chronic diseases such as IBD. In general, an adequate understanding of the safety profile of a drug requires its use in large populations and over a long period of time[1]. Data derived from pre-marketing clinical trials refer to a relatively selected population (not including particularly vulnerable individuals) and for a limited period. Therefore, such initial clinical trials will show frequent adverse events, but not those that are infrequent or specific to particular populations, even if severe. Subsequent, epidemiological surveillance and real-life studies will be essential to know the complete security profile of any treatment.

Biologics have well-defined mechanisms of action, acting selectively on specific targets in the immune response. Theoretically, this would reduce the spectrum of adverse reactions and would make them more "predictable", but this is not always the case. For example, the

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pharmacological target may be expressed in other different cells than those of therapeutic interest, the modulation of a signaling pathway may affect others, sometimes less well known, and there is often no linear correlation between the pharmacokinetic profile of the biologic and the duration and intensity of its effects. Therefore, safety classifications based on mechanisms of action may be more theoretical than real. However, we have been using some of these biological therapies for many years (even almost 25 in the case of anti-TNFs), with millions of patients treated, that implies a broad knowledge of their safety profile.

We will review the safety of the different biologics used in IBD, based on the available data and their particularities. We will place special emphasis on three types of side effects, due to their particular relevance: the *risk of infections* (reactivation of latent infections or disease by obligate or opportunistic pathogens), the *risk of malignancy and the development of immunogenicity and autoimmune complications*. We will address safety in specific situations and how to minimize risks in practice. We will refer the reader to particularly interesting reviews on the subject, which also discuss the safety profile of "new small molecules" with with their potential side effects, out of the subject of this review.

Anti-tumor necrosis factor (TNF)

Anti-TNF drugs work by blocking TNF. They are the first biologics we began to use and, logically, the ones with the most clinical experience. The anti-TNF drugs available in our clinical practice are infliximab and adalimumab (both indicated for Crohn's disease (CD) and ulcerative colitis (UC)) and golimumab (only approved for UC). A fourth anti-TNF agent (certolizumab) is not approved in our setting for IBD. Anti-TNFs have strongly demonstrated clinical efficacy, mucosal healing capacity and probably their ability to modify the natural history of IBD, reducing hospitalizations, and surgeries. There are some subtle differences between the different anti-TNFs that may have implications for efficacy and safety. For example, infliximab is a recombinant chimeric monoclonal antibody, unlike adalimumab and golimumab which are humanized, which may make them less immunogenic. Its mode of production and some aspects of TNF binding are also different.

The safety profile of anti-TNFs is particularly well known; they were first used in 1998 and their real-life side effects are very well defined. They undoubtedly may be considererd as safe drugs, although the risk is always individual and there are specific patients, in whom they may not be the safest biologics.

Infections and anti-TNFs

We have multiple data on the potential relationship of anti-TNFs and infections in IBD, derived from both clinical trials and real-life studies. Some of them, such as two large meta-analyses in CD and UC, showed no higher risk of infections than placebo[2,3]. In the setting of clinical practice studies, the data are not homogeneous. One of the most important, the TREAT registry (*The Crohn's Therapy, Resource, Evaluation, and Assessment Tool*), essentially showed that steroids alone, or in combination with other immunosuppressive agents, especially anti-TNFs, increase the risk of serious infections[4]. Other studies have shown an increased incidence of infections associated with anti-TNF therapy, both reactivation of latent and newly acquired infection, especially in some specific settings. In this regard, data suggest that elderly patient may be at clinically-relevant higher risk, specially if they are under combo therapy with immunosupresants, that is more common when using and anti TNF as a biologic. In the elderly, the risk of infections seems to be higher than in other patients and could also be higher with anti-TNF versus other biologics[5]. The risk and type of infection also varies between patients, situations, and even countries. In our setting, perhaps the most relevant and especially related is tuberculosis, which is also possible in other countries. Let's see the most important infections.

Mycobacterium tuberculosis infection

The most important risk is reactivation of latent mycobacterium tuberculosis infection (TB) when starting anti-TNF treatment. TNF citoquine is key in the control of intracellular germ infections. This is a low but relevant risk, not detected by the initial clinical trials, but in the subsequent open-label use of anti-TNFs. Pharmacovigilance made possible to detect it and establish corrective measures to minimize the risk. Specific recommendations should follow the national guidelines of each country, given that not all geographical areas have the same prevalence of TB, and therefore risk of reactivation of latent TB infection.

In the specific case of Spain, an area with a high prevalence of latent TB infection, GETECCU's latest recommendations are to always perform early screening for latent TB infection and a second mandatory

screening will be added if a risky drug is started. Early screening refers to screening when there is no indication for biologic therapy, ideally at diagnosis of IBD, before the patient is receiving immunosuppression or after the first flare (3 weeks after discontinuation of corticosteroids) and preferably with a low inflammatory burden, in a situation of immunocompetence. It is justified by the possible subsequent need for the use of biologics and/or immunosuppressants. It will consist of an adequate clinical history to detect possible contacts and a *Mantoux skin test* (TST)[6]. Chest X-ray as a screening method should only be performed if the screening is positive or if there has been recent contact with a person with TB, to rule out active infection (Fig. 1). As an initial screening, chest X-ray is not recommended due to its low usefulness and the possibility of confusion in the interpretation of the images. In the latest recommendations in Spain, if latent TB is detected at this time, chemoprophylaxis should not be indicated. To minimize side effects, the treatment it is only indicated if a risky therapy is then going to be started. If in the subsequent evolution, we are going to start a biological or "small molecule", a new screening is obligatory, unless less than 12 months have passed since the initial screening (negative) or if this was not carried out in a situation of immunocompetence. In this case, dual screening with TST and *interferon gamma release assay* (IGRA) is recommended, either simultaneously or no more than 3 days apart (TST causes a boost in IFN-Y production that may alter IGRA test results and lead to false positives). Double screening improves the interpretation of results in some cases. It is considered a positive screen if the induration in the TST is ≥ 5 mm in diameter. This test is very sensitive, but less specific, so in patients vaccinated against TB *(*with *Bacillus Calmette Guerin)* or who have been exposed to Mycobacterium group bacteria, it may cause a false positive and, in these cases, the IGRA test is more specific. On the other hand, TST may be negative in patients on treatment with corticosteroids, thiopurines, methotrexate, anti-TNF, or in a period of active IBD, even without immunosuppressive treatment. Therefore, in these conditions, a "TST booster" or "push effect" would be indicated 1 weeks after the first test. Using this booster, an additional diagnosis of 8-25% of latent TB has been reported. These standards are applicable to all biologicals, although the risk is different between them.

Chemoprophylaxis of latent TB infection will usually be carried out with isoniazid at a dose of 5 mg/kg/day (maximum 300 mg/day), preferably at least 3 weeks before starting anti-TNF and maintained for 9 months. In cases of urgent need to start anti-TNF, both can be started as little as 1 week apart[6].

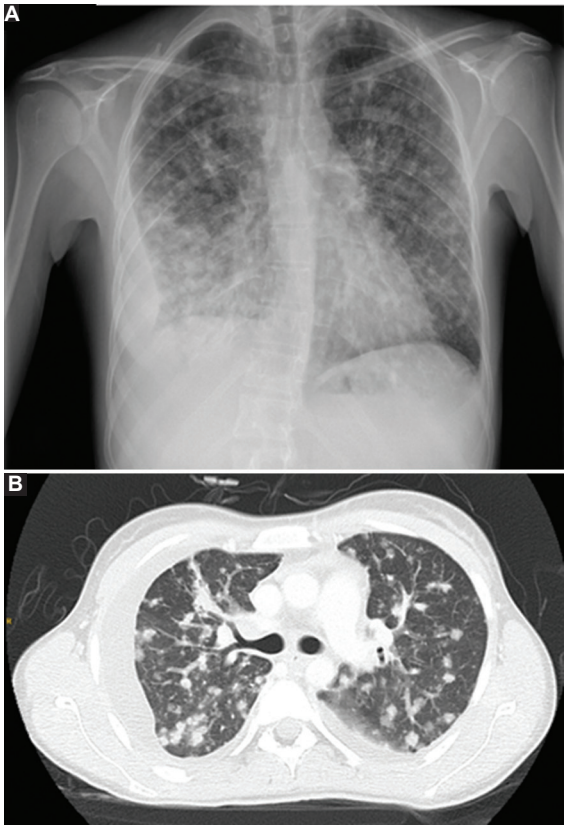

Figure 1. Chest X-ray **(A)** and CT **(B)** of a patient with TB. This case corresponding to a primary TB infection during treatment with infliximab.
CT: computed tomography; TB: tuberculosis.

Hepatitis B virus (HBV)

The risk of HBV reactivation may be higher in patients receiving biologic therapies, although the risk is possibly substantially different depending on the mechanism of action. Isolated cases of fulminant hepatitis due to reactivation have been reported in the case of anti-TNF therapy[7]. In the case of patients with chronic HBV infection (HBs Ag or DNA [+]), who are going to start anti-TNF therapy, it is recommended to start antiviral treatment 2-3 weeks before and mantain it at least 12 months after discontinuation of anti TNF therapy. During anti-TNF treatment, HBV viral load and transaminases should be monitored every 1-3 months, at least until 12 months after discontinuation of biologic therapy, as some HBV reactivations occur after discontinuation of prophylaxis.

In patients with Anti-HBc (+) but without evidence of viral replication, viral replication (HBV DNA [-]), monitoring is recommended during treatment and up to 6 months after the end of immunosuppressive treatment[8,9].

Epstein–Barr virus (EBV)

Primoinfection with this virus under anti-TNF monotherapy does not seem to pose a relevant risk of lymphoproliferative syndrome or hemophagocytic syndrome, as is the case with thiopurines (although the absolute risk is very low). This risk also exists in cytomegalovirus (CMV) negative patients treated with thiopurines. Although it is not a contraindication, in patients with negative serology for EBV or CMV, especially in young patients, we will weigh this risk against the expected benefits of treatment in that particular patient. In these cases, if an anti-TNF is indicated, it may be preferable in monotherapy or if we indicate a combination therapy, chose methotrexate instead of thiopurines[8].

Varicella zoster virus (VZV)

Reactivation of a latent VZV infection, with the production of herpes zoster, is more frequent in patients treated with corticoids, thiopurines, anti-TNF, and especially JAK inhibitors[10]. The new vaccine, made up of fragments of the virus, is now available, at least in Spain, and can therefore be used during these treatments. The avalability and specific indications depend on each health system, but it should be considered in all patients over 50 years of age and before receiving special risk therapy, such as JAK inhibitors. In Spain, this vaccine has been authorized for all patients over 18 years of age who are going to start this treatment.

Human papillomavirus (HPV)

Gynecological cytology is recommended for all women diagnosed with IBD, as they have an increased risk of cervical dysplasia compared to the general population. However, although the connection with anti-TNF therapy has not been established, a risk associated with thiopurines is suggested[11]. The prevention consists in HPV vaccination. In Spain vaccination is universal and free of charge for women born after 1995, although there are differences according to the regions of the country. Although the maximum benefit is before the onset of sexual relations, it is also beneficial for women under 26 years of age and even older, as it could prevent some serotypes that are not present. In patients with IBD, the benefit of vaccination may be even greater[3].

Human immunodeficiency virus (HIV)

HIV serology is recommended before initiating anti-TNF therapy, in addition to assessment of infection status by CD4 levels and viral load. There is no contraindication of using anti-TNF in HIV (+) patients if the viral load is undetectable and the CD4 count is normal (patients in a situation closed to immunocompetence). In those patients controlled with anti-retroviral therapy, no serious infectious complications, CD4 level decrease, or viral load increase have been reported to date. However, CD4 monitoring should be carried out during anti-TNF treatment in addition to the usual monitoring by the physician responsible for HIV infection control. These recommendations apply to all biologics, without finding differences in risk between them.

SARS-COV-2 virus (COVID)

None of the drugs used in IBD have been shown a significant negative impact on the course of COVID. Anti-TNF drugs and tofacitinib have been shown to have a negative impact on the efectiveness of COVID vaccines. This is not the case with ustekinumab (UST) and vedolizumab (VDZ)[12].

Malignancy and anti-TNF

Assessing the potential association of anti-TNFs with the development of malignancies is complicated. One of the reasons is that many studies include patients on combination therapy with thiopurines; an increased risk could be due to one or the other treatment or their combination. In any case, the current evidence suggests that anti-TNF monotherapy is not associated with the development of any type of malignancy, except perhaps melanomas, but data are contradictory[13-16]. In this sense, the current recommendation is applicable to patients under treatment with other immunosuppressants: sunbathe cautiously and under sun protection. If the patient is receiving concomitant thiopurines, it is a good time to consider a dermatological check-up.

The other type of neoplasms that has been linked to anti-TNF therapy are lymphomas. However, the available evidence suggests that it is thiopurines, alone or in combination with anti-TNFs, that may increase this risk. They would act by allowing increased EBV replication, as is the case in transplant-related lymphomas.

It is worth noting one type of lymphoma, particularly rare and severe, which does appear to be related to anti-TNF combined with thiopurines: hepatosplenic T-lymphoma. They are not clearly related to EBV and have been described in young patients, especially males, and in combination treatment with anti-TNF and azathioprine for a prolonged period of time (generally more than 2 years). It is therefore recommended, in this specific population, to limit the duration of combination therapy or to combine anti-TNF with methotrexate[17].

The use of biologics in patients with a history of tumors will take into account the type of neoplasm, the specific characteristics of the patient, and the time since diagnosis. All these factors, in addition to the drug being considered, will influence the final decision. Sometimes, the assessment with the oncologist can be decisive. In the specific case of anti-TNF drugs, it does not seem to be the best biologic in a patient with a history of melanoma and perhaps not even lymphoma.

Immunological reactions and anti-NF reactions

Anti-TNF drugs, and all biologics in general, can generate an immunological response against them by the patient, as they are potentially antigenic molecules. Thus, immunogenicity of anti-TNF drugs is relatively common with some differences between them. The development of anti-TNF antibodies may lead to secondary loss of efficacy, which may be caused by various mechanisms (immunomediated or non-immunomediated pharmacokinetic and also pharmacodynamic failure). Determination of serum drug and anti-drug antibody levels will help in making the decision between therapeutic alternatives. The evidence in this regard is more consistent in the case of patients treated with anti-TNF drugs (especially infliximab and adalimumab) than with other biologics. Another adverse effect associated with the development of antibodies, although not in all cases since other immune mechanisms may also be possible, are reactions to administration. They are more frequent with infliximab than with adalimumab, as well as being potentially more severe, due to intravenous use (infusion reactions). Reactions to subcutaneous biologics are essentially injection site reactions.

There are some immune-mediated adverse events that can be called paradoxical reactions. They are called this way, because they paradoxically produce or worsen a condition, for which they are usually effective. The most frequent seems to be paradoxical psoriasis (development psoriasis as a consequence of anti-TNF treatment). According to some series, with anti-TNF therapy, it could affect up to 5% of patients[18,19]. Others are also possible, even including paradoxical IBD. These paradoxical reactions are usually a class effect and are often repeated with drugs in the same therapeutic group.

Finally, anti-TNF drugs can trigger demyelinating disease or pharmacological lupus-like syndrome. Both of them are rare effects, but more likely to be found with anti-TNF therapies than with other biologics[20,21]. In fact, multiple sclerosis is a contraindication for the use of anti-TNF and not the other biologics.

Other side effects and anti-TNFs

They are contraindicated in subjects with moderate to severe heart failure (NYHA III-IV). Cases of liver disorders have been reported, with isolated cases of autoimmune hepatitis and more rarely liver failure[22,23]. Occasionally, cytopenia attributable to treatment may occur[20,24].

Ustekinumab

Anti-TNFs have limitations, both in efficacy and safety, and biologics with different therapeutic targets are being investigated, such as UST and VDZ, already widely used in real life. UST is a fully human monoclonal antibody of the IgG1 type, directed at the p40 subunit, shared by interleukins 12 and 23, inhibiting the binding of both to the receptors expressed on the surface of CD4 T lymphocytes, natural killer, and antigen-presenting cells. In other words, they inhibit the immune response mediated by IL-12 and IL-23. It is indicated in moderate to severe flares of CD and UC with no response to “conventional” or anti-TNF therapy (primary non-response or secondary loss of response) or when these are contraindicated. In clinical practice, it is usually used as a second-line biologic. However, it may have additional advantages, specially in relation to its safety, making it an excellent first-line option in some specific patients.

Infections and ustekinumab

In IBD clinical trials, UST showed no increased risk of infections against placebo, with similar rates of severe infection[25]. We also have extensive and longer-term data in other diseases where UST has been in use for many years, with no special safety signals[26]. Indeed, in these diseases, the studies suggest the greater safety of UST in comparison with biologics (such as anti-TNF), at least for some side effects. It is true that the data on safety in IBD are not as extensive

as with anti-TNFs, but they are growing every day and allow us to confirm the safety of the treatment, with more and more data every day even in special populations populations.

In early 2022, an observational study of more than 20,000 IBD patients was published comparing the risk of infection with UST or tofacitinib versus those treated with anti-TNF. The risk with UST was lower compared to anti-TNF, while tofacitinib had a similar risk to anti-TNF[27]. These differences are likely to be clinically relevant, at least in more vulnerable patient subgroups, such as the elderly, especially if concomitant immunosuppressants are associated with anti-TNF.

In the case of TB, although isolated cases have been reported, it is very likely that the risk of reactivation of latent TB infection is much lower than in the case of anti-TNF drugs. Even so, the recommendations about prophylaxis when UST is to be initiated are exactly the same[26].

Something very similar happens with HVB: the risk could be lower than with anti-TNF drugs, but some isolated cases of reactivation have been described, so the recommendations are the same[28]. All patients should be vaccinated at diagnosis and, if not already done, ideally before starting treatment with UST. All recommendations are overlapping (*see anti-TNF section*). In relation to HIV, the recommendations are also the same as with anti-TNF. In the case of herpes zoster, the risk with UST seems lower than with anti-TNF or other drugs, but vaccination with the new vaccine will probably be recommended (it will probably be imposed on all patients > 50 years). The severity of COVID infection, and the efectiveness of its vaccines, is not affected by concomitant treatment with UST[12].

Malignancy and ustekinumab

The available data in IBD and other diseases suggest that UST does not increase the risk of neoplasms[26,29]. In fact, due to the mechanism of action and the data available, UST could be specially a safe biologic in patients with previous neoplasms. In any case, a cautious approach should be taken, so what has been described for anti-TNF drugs is applicable in practice with UST behind some technical nuances.

Immunological reactions and ustekinumab

UST have also shown lower immunogenicity than anti-TNF drugs; less than 3% of patients developed antibodies to UST, often with no decrease in its efectiveness. In comparative studies in IBD, UST has been shown to be the least immunogenic biologic[30]. Infusional reactions are very rare, both after iv infusion and at the subcutaneous injection site[28]. Therefore, pharmacokinetic monitoring, especially proactive monitoring, seems less necessary and useful than with anti-TNFs.

Paradoxical reactions also seem to occur less frequently, although some have been reported, including worsening of psoriasis in an isolated patient[31].

Other side effects and ustekinumab

UST is not contraindicated in patients with multiple sclerosis or heart failure. The reported cases of hepatotoxicity are anecdotal and generally mild. No relevant hematological alterations have been reported in clinical trials[26,28,32].

Vedolizumab

The other non-TNF biologic that we use extensively in IBD is VDZ. It is a humanized IgG1 monoclonal antibody that blocks the $\alpha 4\beta 7$ integrin, a protein on the surface of human lymphocytes that allow their exit from the vascular stream to the gastrointestinal tract. It is produced using recombinant DNA technology in Chinese hamster ovary cells.

Its indication is the same as that of UST and it is also often used as a second-line biologic after anti-TNF drugs. Although, it may have additional advantages, specially in relation to its safety, which are clinically relevant in some specific patients, like its selectivity in the digestive tract.

Infections and vedolizumab

Many studies provide data on the good safety profile of VDZ, particularly in relation to infections. Clinical trials did not detect an increased risk of infections in patients treated with VDZ compared to those receiving placebo. In a meta-analysis of these trials, the rate of infections with VDZ was even lower than with placebo[32]. Real-life studies also show very low infection rates, which may be lower than during anti-TNF treatment[33]. Importantly, there have been no cases of progressive multifocal leukoencephalopathy due to reactivation of JC virus infection. This severe adverse event effect led to the abandonment of the approval in CD of natalizumab, another anti-integrin biologic with a similar mechanism of action, but without the intestinal selectivity of VDZ[34]. Among the infections described,

enteric infections may be more frequent, precisely due to the intestinal selectivity of VDZ.

As with all other biologic treatments, we should request serology for EBV, CMV, HIV, HBV, and HCV and rule out latent TB in all patients starting treatment with VDZ. However, the risk of reactivation of all these diseases seems very low.

Although it is considered a particularly safe drug in relation to infections, the available data and common sense advise against its use during severe active or opportunistic infections. The same is true for the administration of live microorganism vaccines under therapy with this drug, with many experts considering therapy with VDZ as a contraindication at this moment[27].

Malignancy and vedolizumab

The available data do not suggest an association with any particular neoplasm[35,36]. Although VDZ could be a specially safe biologic treatment, the same recommendations as with all biologics should be maintained. Due to its mechanism of action (it acts primarily on the digestive tract), there were some initial doubts about a potential increased risk of gastrointestinal tumors, but this has not been demonstrated in any study[37].

Immunological reactions and vedolizumab

VDZ, like UST, is less immunogenic than anti-TNF drugs. Therefore, antibody formation and secondary loss of immune-mediated efficacy, is low. Infusional reactions are very rare and do not usually require discontinuation of treatment[32]. Paradoxical reactions are also very rare, although some have been described[38]. The use of VDZ has been associated with the development of arthralgias (de novo or worsening of previous ones), although with contradictory data. The cases of lupus described with VDZ are anecdotal[32].

Other side effects and vedolizumab

Vedolizumab is not contraindicated in heart failure or in patients with multiple sclerosis[27].

How can we optimize the safety of biologics?

Appropriate use of these drugs will minimize their risks and optimize their outcomes, through a "triple" strategy of the primary, secondary, and tertiary prevention (Table 1). The first step in limiting the risks of biologics is to use them in the right patient. It is a question of balancing efectiveness and safety in the individual patient. Sometimes, more risk must be assumed for the expected benefits, while, in others, this will not be the case. The clinical scenario is key, and the clinician's decision is difficult and complex, as comparative studies between different drugs are very scarce and do not address many scenarios in the clinical practice. Some of these are mentioned below.

Table 1. Suggested key points for optimizing the safety of biological treatment with a three-steps strategy

Prior to initiating treatment (primary prevention)	Right indication, patient and timing
	Patient information and shared decision-making
	Complete vaccination schedule. Consider chemoprophylaxis of latent infections (TB and HBV among others, see text). Rule out other potential contraindications (neoplasms, autoimmune diseases, co-morbidities, pregnancy, active infection)
	Be comprehensive and systematic: use checklists (*example: GETECCU checklist for anti-TNF use*)
	Special caution in specific populations: age and comorbidity, history (mainly neoplasms), "other" (children, vaccines, latent infections, specific contraindications)
During treatment (secondary prevention, see table)	Monitoring (analytical and clinical, informing the patient and where it could be completed, ensuring prompt access to consultations) and early diagnosis strategy
Management of complications (Tertiary prevention)	Adequate and early treatment of adverse effects (*see specific references*[49])

Before starting treatment, a key aspect that is sometimes forgotten is to inform patients and their relatives, so that they can make a shared decision. When considering the use of a biologic, we must inform the patient of its benefits and risks and why we are recommending it. As support, we can use online platforms that provide patients with the best possible information, while allowing them to take the time that is sometimes necessary to make the best possible decision. In this sense, we clearly recommend as a website in spanish: www.educainflamatoria.com, a Spanish website. Everything should be reflected in the clinical history. In summary, to minimize the risk of infections, and for all biologics, it is recommended:

- Screening for latent infections, and treatment if required serologies including HIV, HBV, HCV, EBV, CMV and VZV, as well as screening for latent TB, as previously described.
- Updating of the vaccination schedule according to local standards, through specific interdisciplinary circuits.
  Treatment with anti-TNF drugs has been shown to affect the efectiveness of some vaccines. Although there is less data, VDZ and UST could also affect the efectiveness of vaccines. In the case of COVID, we already know that its negative impact on vaccine efectiveness is not relevant, unlike anti-TNF drugs. In the case of VZV, the severity increases with age, and the new viral fragment vaccine is recommended if ≥ 50 years old and always before starting a JAKi, due to its special risk. This risk is also higher with anti-TNF drugs than with other biologics.
  Regardless of the biologic drug used, it is contraindicated to administer live virus vaccines during treatment. If this type of vaccine is necessary, we will wait 1 month from vaccine administration until the start of biologic treatment or 3 months from biologic discontinuation until the vaccine is administered. Other types of vaccines (killed virus, non-replicating vectors, and virus fragments) can be administered at any time. Vaccination should be done in a situation as close to immunocompetent as possible, often at diagnosis.
- In specific cases, prophylactic treatment before infection may be indicated, such as in patients with perianal abscesses in whom we choose to start anti-TNF treatment or in patients under triple immunosuppression (corticosteroids, thiopurines, methotrexate, or biological treatment) to prevent Pneumocystis infection.

To be methodical and not to forget any relevant aspect in these patients, it is useful to use checklists before starting the treatment, common to all patients and biologics. Versions of these have been developed by some institutions and can be found at their websites, being the one of GETECCU a good example (https://geteccu.org/formacion/documentos-de-posicionamiento).

During the follow-up of these patients, we will monitor them through the appropriate visits and examinations, generally very similar but adapted to the patient and biologic, in terms of which ones and how often, to avoid/early detect adverse events (Table 2).

In terms of use in special populations, it is also worth highlighting some of them:

- Pregnancy and lactation. IBD activity is the main factor associated with the development of maternal-fetal complications during pregnancy. Therefore, "timing" the pregnancy, being in remission and maintaining it during gestation is of vital importance for both, mother and fetus. Biological drugs cross the placenta, especially in the third trimester.
  The data available with anti-TNF is already relatively large and shows no evidence of side effects for the fetus and newborn. The safety of UST and VDZ during pregnancy is logically less well known, although the available data are similar.
  Prospective clinical practice registries are needed to better understand the safety of biologic drugs used in IBD during pregnancy and later in the child. We would like to highlight the DUMBO registry, currently underway, with more than 500 pregnancies included, which will undoubtedly provide necessary evidence in these scenarios. It is a prospective spanish registry, in which pregnancy and the child are followed up to 4 years of age. Preliminary data suggest that all biologics appear safe for pregnancy and the child[39]. As for breastfeeding, the data with anti-TNF suggest that they are safe and the vast majority of experts authorize breastfeeding[40-42]. Although biologics are large proteins excreted into breast milk, are not absorbed through the enteric route. However, incomprehensibly, a recent EMA alert suggests avoiding breastfeeding in women who are receiving anti-TNFs or have received them in the third trimester of pregnancy (see: https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-infliximab-remicade-flixabi-inflectraremsima_en.pdf). In any therapeutic decision before and during pregnancy, informing the mother and shared decision-making is even more essential to get it right. The time we spend informing the patient can be key to avoid withdrawing necessary treatments due to unfounded fear about their safety.
- Elderly patient. Its definition varies between > 60 or > 65 years, but frailty associated with concomitant diseases may be more important than age. There are an increasing number of elderly patients with IBD, either because they are then diagnosed or after IBD diagnosis become elderly. In these patients, the essential risks of any drug with immunosuppressive effects are infections and tumors. Other particularities are polypharmacy (possibility of interactions), functional problems (mobility and abilities), and increased vascular risks. Even age > 50 years coupled with the use of immunomodulators is considered a risk factor for opportunistic infections. These

Table 2. Proposal for follow-up and monitoring of patients under biological therapy

Biological type	Analyses/other required	Periodicity of checks	Some practical aspects
Anti-TNF	CBC/biochemistry/transaminases/CRP/ calprotectin. Levels of anti-TNF and anti-TNF Ac: – Induction: ideally weeks 2-6-12 for early optimization, otherwise at the end of induction – In case of secondary loss of response – If remission is maintained, annual Quantiferon annually and on change of biologic Anti-HBs annual. Dermatology, especially if you have a light skin phototype.	Two quarterly visits/analyses at the start of treatment. Quarterly during the following year. Subsequently every 6 months.	Face-to-face medical visits at the start of treatment and for 1 year; if remission is maintained and patient prefers consider option of telematic or alternate visits (minimum annual face-to-face visit).
Ustekinumab	CBC/biochemistry/transaminases/CRP/ calprotectin.	Two quarterly visits/analyses at the start of treatment. Quarterly during the following year. Subsequently every 6 months.	Face-to-face medical visits at the start of treatment and for 1 year; if remission is maintained and patient prefers consider option of telematic or alternate visits (minimum annual face-to-face visit).
Vedolizumab	CBC/biochemistry/transaminases/CRP/ calprotectin.	Two quarterly visits/analyses at the start of treatment Quarterly during the following year. Subsequently every 6 months.	Face-to-face medical visits at the start of treatment and for 1 year; if remission is maintained and patient prefers consider option of telematic or alternate visits (minimum annual face-to-face visit)
Tofacitinib (*)	Mandatory analytical monitoring (lymphocytes, hemoglobin, and lipids), with specific recommendations for action Blood count and biochemistry with lipid profile at one and 2 months. Subsequent blood count/biochemistry/transaminases/PCR/ calprotectin. Obligatory monitoring of specific adverse effects: thromboembolic disease, herpes zoster infection. MACEs. Dermatology, especially if you have a light skin phototype.	Blood count and biochemistry with lipid profile at 1 month and 2 months. Two quarterly visits/analyses at the start of treatment Quarterly during the following year. Subsequently consider spacing to every 5-6 months.	Face-to-face medical visits at the start of treatment and for 1 year; if remission is maintained and patient prefers consider option of telematic or alternate visits (minimum annual face-to-face visit). There are specific contraindications to initiating tofacitinib, as well as specific recommendations for patients over 65 years of age (see label, black-box) or with specific pathologies.

*In this table we include the new small molecules, specifically the only one approved, to compare the need for monitoring, which is higher in this case. This is a proposal, the authors' opinion, and includes modifications to the COVID pandemic scenario.
MACEs: mayor adverse cardiovascular events.

include atypical bacterial infections, aspergillosis, coccidioidomycosis, legionellosis, cryptococcosis, nocardiosis, toxoplasmosis, pneumocystis jirovecci pneumonia, listeriosis, and Histoplasma histoplasma capsulatum intections. In these patients, steroids are associated with additional additional adverse events and maintaining them when they are ineffective or using them to avoid a biologic, is often a poor decision. Thiopurines are also not a good alternative in this population, especially in terms of safety, and JAK inhibitors are contraindicated. Among the biologics, anti-TNF drugs are effective in the elderly but may have greater risks in relation to infections, than UST and VDZ[43]. Although the data are not definitive, UST and VDZ appear to be as effective as in younger population and without additional risks. Recent data from Spanish registry ENEIDA show that it is clear in the case of UST in the elderly (in press). In any case, in the elderly population requiring biological treatment, we will be exhaustive in the prevention of infections and in the monitoring of potential side effects. This is a group of patients, in whom UST and VDZ could be safer than anti-TNFs from a "clinically relevant" point of view.

– Patients with a history of previous malignancy. Another group of patients in whom the decision to initiate treatment is particularly complex and needs to be individualized and interdisciplinary (Table 3). We must chose when and which treatment to use considering the type of tumor, its stage and the activity

Table 3. Risk of recurrence of different tumors and general recommendations for the use of biologic and immunosuppressive treatments in patients with IBD and a history of cancer

Tumors at low risk of recurrence (0-10%)	Tumors at medium risk of recurrence (10-25%)	Tumors at high risk of recurrence (>25%)
Lymphoma Testicle Cervix Thyroid	Endometrium Wilms' tumor Colon Mama Prostate	Bladder Kidney Skin Sarcoma Myeloma
Recommendation	**Recommendation**	**Recommendation**
Avoid immunosuppression, up to 1 year after remission.	Avoid immunosuppression, if possible, until 2 years after remission.	Avoid immunosuppression, if possible, until 5 years after remission.

Note: all decisions should be based on the individual patient's characteristics.

Table 4. Recommendations for the use of specific biologics in patients with a history of malignancy

Type of neoplasm	Preferably use	Preferably do not use	Consider with caution
Hematological (leukemia and lymphomas)	VDZ UST	Thiopurines	Anti-TNF, MTX, tofacitinib
Non-melanoma skin cancer	VDZ, UST Anti-TNF, MTX	Thiopurines	Tofacitinib
Melanoma	VDZ, UST, thiopurines	Anti-TNF	MTX
Solid tumors	Any biological similar evidence		Lower evidence with tofacitinib
Genitourinary or cervical	VDZ, UST, anti-TNF, MTX	Thiopurines	Lower evidence with tofacitinib

For specific therapeutic management in the setting of active neoplasm during treatment with biologics, we suggest reading the recent review by Click and Regueiro[47].
VDZ: vedolizumab; UST: ustekinumab; MTX: methotrexate.

and characteristics of IBD in the individual patient[44] (Table 4).

In the future, we will undoubtedly have better drugs that will allow us to break the therapeutic ceiling in IBD and personalize treatment. For the time being, while awaiting these achievements, which are still a long way off, we must optimize the biologics available to make the most of them. Doing your best as a practicing physician, applying recommendations based on the best available evidence, is still the key at the present time to achieve the best therapeutic goals for the individual patient, including efectiveness and safety.[45,46].

Conflicts of interest

None.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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