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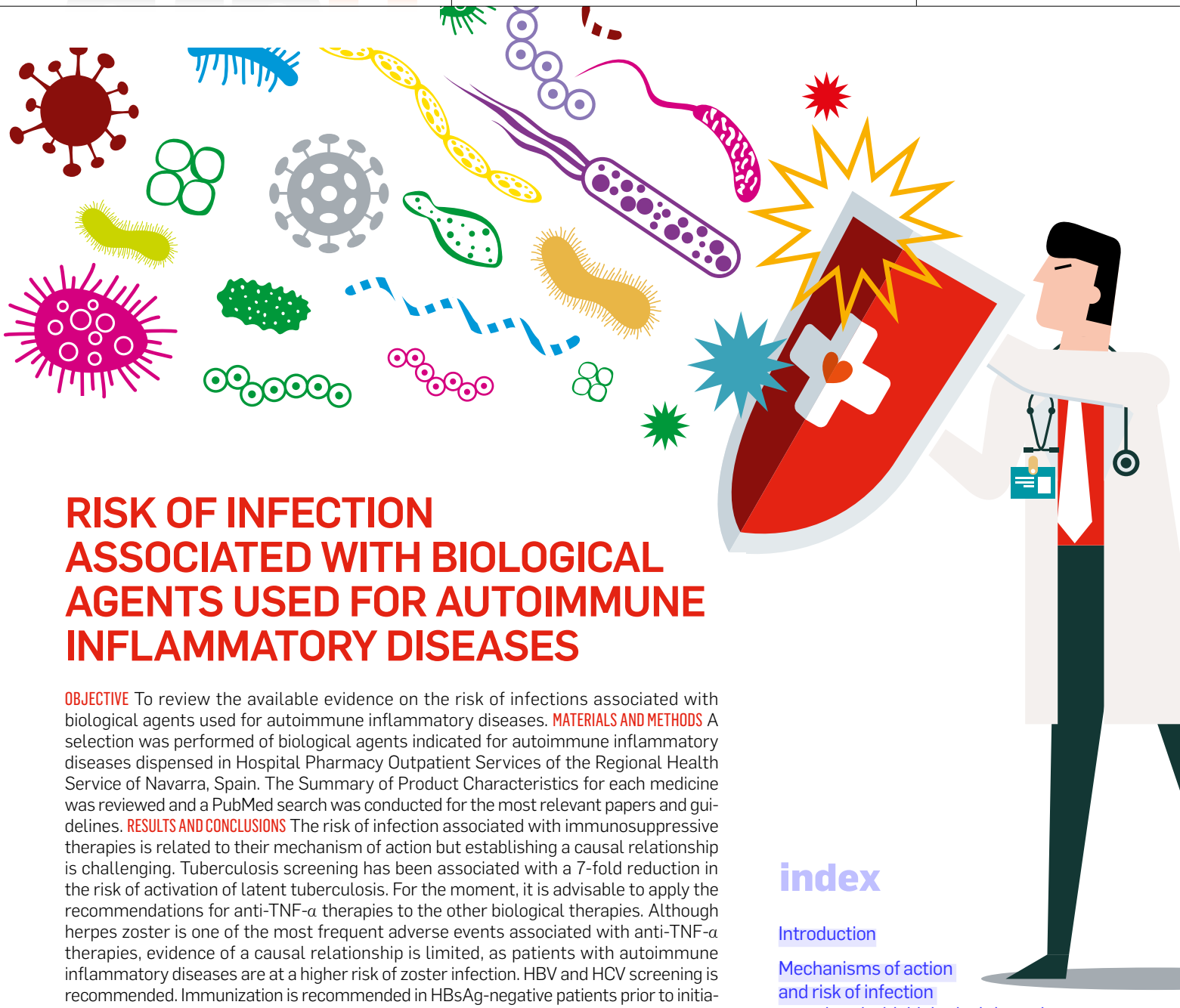

RISK OF INFECTION ASSOCIATED WITH BIOLOGICAL AGENTS USED FOR AUTOIMMUNE INFLAMMATORY DISEASES

OBJECTIVE To review the available evidence on the risk of infections associated with biological agents used for autoimmune inflammatory diseases. MATERIALS AND METHODS A selection was performed of biological agents indicated for autoimmune inflammatory diseases dispensed in Hospital Pharmacy Outpatient Services of the Regional Health Service of Navarra, Spain. The Summary of Product Characteristics for each medicine was reviewed and a PubMed search was conducted for the most relevant papers and guidelines. RESULTS AND CONCLUSIONS The risk of infection associated with immunosuppressive therapies is related to their mechanism of action but establishing a causal relationship is challenging. Tuberculosis screening has been associated with a 7-fold reduction in the risk of activation of latent tuberculosis. For the moment, it is advisable to apply the recommendations for anti-TNF-α therapies to the other biological therapies. Although herpes zoster is one of the most frequent adverse events associated with anti-TNF-α therapies, evidence of a causal relationship is limited, as patients with autoimmune inflammatory diseases are at a higher risk of zoster infection. HBV and HCV screening is recommended. Immunization is recommended in HBsAg-negative patients prior to initiation of a biological therapy, whereas HBsAg-positive patients must receive prophylaxis. Live attenuated vaccines are contraindicated during the use of biological treatment, and influenza and pneumococcus immunization are recommended for all patients receiving biological therapies. HIV screening, pregnancy testing and assessment of other conditions such as heart failure, cytopenias, interstitial lung disease, demyelinating disease, or tumor disease are recommended prior to the start of the therapy. KEYWORDS Biological agents, inflammatory diseases, tuberculosis, infectious risks, immunization.

IRATI IRIGOYEN RODRIGUEZ
OIHANE GOÑI ZAMARBIDE
Subdirectorate of Pharmacy
Medicines Advice and Information Service. Navarre Health Service

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Introduction

According to the European Medicines Agency, biological medicines contain active substances from a biological source, such as living cells or organisms and are often produced by cutting-edge technology. Exceptions include microbial metabolites such as antibiotics, amino acids, carbohydrates, and other low molecular weight substances.

These therapies are designed to specifically act on a therapeutic target significantly involved in the pathogenicity of the disease[1].

This review is focused on subcutaneous biological therapies dispensed by the Hospital Pharmacy Outpatient Services. It is relevant to note that, although infliximab (a tumor necrosis factor [TNF] antagonist) was included in most comparative studies, this medicine was not included in our review, as it is an intravenous therapy.

Mechanisms of action and risk of infection associated with biological therapies

The risk of infection associated with immunosuppressive therapies is related to their mechanism of action. Rare infectious complications are generally observed during post-marketing surveillance (eg, tuberculosis activation with anti-TNF-α therapies or progressive multifocal leukoencephalopathy due to natalizumab). Therefore, it is important to consider the risk of infection even if it has not been observed in pivotal trials[2].

In clinical practice, establishing a causal relationship between a drug and a higher incidence of infections is challenging due to the numerous factors that contribute to infectious processes. These factors include having received or being receiving concomitant immunosuppressive therapy, the nature and stage of disease, the duration of therapy, and the cumulative dose of the drug[2,3]. It is important that the patient understands the most frequent risks and is aware of the signs of infection that would require further investigation.

Active systemic or local infection must be excluded before a biological therapy is initiated, as infection is a contraindication2,4. In patients with a history of recurrent infection or sepsis, careful risk/benefit analysis and close monitoring are necessary. Apart from interfering with acute responses, biological treatments may also reduce the response to latent or chronic infections[2].

Anti-TNF-α therapies: adalimumab, golimumab, certolizumab pegol and etanercept

Tumor necrosis factor-α (TNF-α) is involved in adaptive immune response and takes part in the development of granulomas and phagosomes. Therefore, anti-TNF-α therapies are expected to increase susceptibility to intracellular pathogens. As mycobacteria survive in the macrophages of patients with latent tuberculosis anti-TNF-α therapies may cause a reactivation or dissemination of tuberculosis. In addition, anti-TNF-α therapies may cause neutropenia, thereby increasing the risk for invasive fungal infection. In contrast, TNF-α is not involved in innate immune response against extracellular bacterial pathogens[5].

A systematic review published in 2015 revealed that standard- and high-dose anti-TNF-α therapies increase the risk of serious infection compared with conventional disease-modifying antirheumatic drugs[6].

Interleukin (IL) inhibitors

A recent systematic review assessed the safety of different anti-interleukin drugs used for a variety of indications (eg, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and lupus). The median duration of placebo-controlled studies was 24 weeks and revealed a statistically significant two-fold increase in the risk for serious infection associated with the use of anti-interleukin therapies [OR (95%CI): 1.97 (1.58 to 2.44)] (NNH: 67). A higher incidence of opportunistic infections was also observed in studies with a median duration of 54 weeks [OR (95%CI): 2.35 (1.09 to 5.05) (NNH: 250)][4].

Anti-IL-12/23 drugs: ustekinumab

IL-12 and IL-23 mediate innate immune response by increasing the cytotoxic activity of Natural Killer cells and induce the polarization of CD4+ T helper cells. Hence, ustekinumab is expected to increase susceptibility to intracellular infections. On the other hand, IL-23 is responsible for T helper-17 differentiation and maintenance. As a result, patients receiving ustekinumab are likely to be more susceptible to fungal infections7. Although the risk of fungal infection is mentioned in the product information , mycotic infections are not listed among the most frequent adverse reactions. Vulvovaginal mycotic infection is mentioned as a rare adverse reaction[8].

Anti-IL-23 agents: guselkumab and tildrakizumab

These agents are specific IL-23 inhibitors so, theoretically, they may not produce adverse events that have been associated with other mechanism of action9,10. Respiratory tract infections are included in the list of the most frequent adverse reactions of these therapies in the Summary of Product Characteristics[11,12].

Anti-IL-17 agents: secukinumab, ixekizumab and brodalumab

IL-17 is a cytokine with pro-inflammatory effects. The clinical impact of blocking IL-17 can be deduced from the effects of primary immunodeficiencies caused by nonsense mutations [autoimmune polyendocrinopathy syndrome type 1 (APS-1)]. Thus, patients with APS-1 are more susceptible to mucocutaneous infections by *Candida spp* (rarely disseminated or invasive). Apparently, the role of IL-17 in the immune function is not as relevant as that of TNF-α, and secukinumab has no effects in vitro on *Mycobacterium tuberculosis* dormancy within granulomas[7].

No statistically significant differences have been observed between secukinumab and etanercept in the overall incidence of infections[13]. Although secukinumab is associated with a higher dose-dependent incidence of *Candida spp* infection compared with etanercept, all infections were mild mucocutaneous infections and are not listed among the most common adverse effects of these drugs (except for dermatophytosis associated with brodalumab)[7].

Anti-IgE: omalizumab

Omalizumab binds to the IgE domain and prevents it from binding to the high-affinity IgE receptor (FceRI) in basophils and mast cells, thereby reducing the volume of available free IgE to trigger the allergic cascade. The relevant role of IgE in immune response to parasites suggests that omalizumab may increase susceptibility to parasitic infections[7].

Active infection must be excluded before a biological therapy is initiated, as it is a contraindication

Pivotal trials and a post-marketing study on different indications did not demonstrate any increase in the frequency of adverse reactions related to immunosuppression. Only a trial conducted in patients with idiopathic urticaria showed an increase in the rate of upper respiratory tract infections with respect to placebo[7].

In patients with a high chronic risk of helminthiasis, a placebo-controlled study in allergic patients revealed a slight increase in the incidence of infection in patients who received omalizumab. The proportion of helminthiasis in the overall clinical trial programme, where this type of infection was not screened for, was below 1 in 1,000 patients[14].

Anti-IL-5 agents: mepolizumab, reslizumab and benralizumab

IL-5 is a glycoprotein characterized by its capacity to contribute to the proliferation and differentiation of eosinophils and, to a lesser extent, B-cells. Eosinophilia is a distinctive characteristic of parasite infections and infections by some protozoa.

A systematic review revealed that mepolizumab is associated with an increase in respiratory tract infections compared with placebo. However, no cases have been reported of parasite infection related to the use of these drugs[7]. In the Summary of Product Characteristics, infections appear as frequent adverse reactions.

Anti-IL-6 agents: tocilizumab, sarilumab and siltuximab

Cytokine IL-6 is involved in inflammation, immune system regulation and tissue regeneration. IL-6-linked primary immunodeficiencies are associated with a higher susceptibility to microorganisms such as Escherichia coli, Staphylococcus aureus and Streptococcus intermedius[7].

Although the risk for serious infection has been reported to be relatively low in clinical trials[15], the risk for severe opportunistic and bacterial infection in long-term safety studies has been found to be similar or even higher than with other treatments such as anti-TNF-α[16].

Close monitoring is required for the early detection of serious infection, and the signs and symptoms of acute inflammation can be reduced by suppressing acute phase reactants[17].

Anti-IL-1 agents: anakinra and canakinumab

IL-1 is a very active pro-inflammatory cytokine that stimulates the production of prostaglandins and nitric oxide and induces the synthesis of pro-inflammatory cytokines such as IL-1b and IL-18[18].

The available evidence has been mostly generated from placebo-controlled clinical trials assessing the effectiveness of anakinra for rheumatoid arthritis and canakinumab for gout. An increase in the incidence of mild-to-moderate infections has been documented. The occurrence of these adverse events seems to be induced by the mechanism of action of anti-IL-1 agents. Thus, the CANTOS clinical trial (anakinra vs placebo), which included patients with a history of myocardial infarction (without autoimmune disease), also showed an increased incidence of dose-dependent neutropenia and a significantly higher frequency of fatal infection or sepsis compared with placebo[19].

The cumulative rate of serious infections is similar to that observed with other disease-modifying antirheumatic drugs such as tocilizumab, and the data obtained indicate that it keeps constant in the long term[7].

Anti-IL4: dupilumab

Dupilumab is a human IgG4 recombinant monoclonal antibody that inhibits interleukin-4 and interleukin-13 signaling[20]. Placebo-controlled clinical trials have not shown an increase in the risk for infection or a higher incidence of serious or opportunistic infections. These studies demonstrated a slightly higher rate of infections by herpes simplex virus and a lower incidence of serious herpes zoster infection[21,22]. The Summary of Product Characteristics (SmPC) does not indicate that previous screening is needed before treatment is initiated, except on suspicion of helminth infection. If confirmed, it is recommended to treat the infection prior to the start of the biological treatment.

Human IgG1 monoclonal antibody: belimumab

Belimumab inhibits B-cell survival and reduces their differentiation into immunoglobulin-producing plasma cells[23].

Mild-to-moderate infections were the most frequent adverse events documented in clinical trials and clinical trial extensions, with a total follow-up period of seven years. The reported incidence of opportunistic infections is 2.3%[24]. In a phase 2 study with a 13-year follow-up, the incidence of infections (including opportunistic infections) was 5.1/100 patients/year[25]. Research has not been conducted in patients with human immunodeficiency virus (HIV), history or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). In addition, the risk of using belimumab in patients with active or latent tuberculosis is unknown. Therefore, a risk/benefit analysis is recommended prior to the start of treatment[23].

Anti-CD28 human monoclonal antibody: abatacept

Abatacept inhibits the activation of T-lymphocytes that express CD28, thereby reducing the production of TNF-α, interferon-α and IL-2[26].

In clinical trials, the rate of infection associated with the use of abatacept is similar to that observed in patients treated with methotrexate[27] and the incidence of serious infections linked to the use of abatacept is significantly lower than with certolizumab[28].

This agent has been associated with a lower risk of infection requiring hospitalization compared with anti-TNF-α. However, a study suggested that this difference was due to the use of infliximab and was not significant when compared with adamilumab and etanercept[29].

Which are the most serious infectious risks?

Tuberculosis

Most evidence has been generated in short-term clinical trials conducted in regions with a low incidence of tuberculosis (USA and Western Europe). In addition, these studies did not have the power to detect less frequent adverse effects. In the most recent clinical trials, tuberculosis screening was performed and patients with latent tuberculosis were excluded. This has resulted in a decreased incidence of drug-related tuberculosis[15,30]. Tuberculosis screening has been documented to reduce the risk of reactivation of latent tuberculosis by up to 7 -fold[31].

Table 1. Main adverse effects of biologicals.

Drug		Indication	Tradename (Year of approval)	Main adverse reactions
ANTI-TNF-α	Etanercept	· Rheumatoid arthritis · Juvenile idiopathic arthritis · Psoriasic arthritis · Axial spondylitis · Ankylosing spondylitis · Plaque psoriasis	Enbrel® (2002); Benepali®; Erelzi®	Infections, reactivation of tuberculosis, psoriatic changes in the skin, exacerbation of demyelinating diseases, induced lupus, nonmelanocytic skin cancer.
	Adalimumab	· Juvenile idiopathic arthritis · Axial spondyloarthritis · Psoriatic Arthritis · Psoriasis · Hidradenitis suppurativa · Crohn disease · Ulcerative colitis · Uveitis · Pediatrics: Plaque psoriasis, Uveitis, Crohn disease	Humira®(2015); Amgevita®; Hulio®; Hyrimoz®; Imraldi®	
	Certolizumab Pegol	· Rheumatoid arthritis · Psoriasic arthritis · Axial spondylitis · Plaque psoriasis	Cimzia®(2009)	
	Golimumab	· Rheumatoid arthritis · Juvenile idiopathic arthritis · Psoriasic arthritis · Axial spondylitis · Ulcerative colitis	Simponi® (2009)	
ANTI-IL-12/23	Ustekinumab	· Psoriasic arthritis · Common psoriasis · Ulcerative colitis · Crohn's disease	Stelara®(2009)	Infections (especially of the upper respiratory tract), oropharyngeal pain, dizziness, headache, diarrhea, nausea, itching, arthralgia, and myalgia.
ANTI-IL-23	Guselkumab	· Plaque psoriasis	Tremfya®(2017)	Infections of the upper respiratory tract, herpes simplex, headache, gastroenteritis, nausea, diarrhea, back pain.
	Tildrakizumab	· Plaque psoriasis	Ilumetri®(2018)	Infections of the upper respiratory tract, headache, gastroenteritis, nausea, diarrhea, back pain.
ANTI-IL-17	Secukinumab	· Psoriasic arthritis · Plaque psoriasis · Ankylosing spondylitis	Cosentyx®(2015)	Infections (especially of the upper respiratory tract), rhinorrhea, diarrhea.
	Ixekizumab	· Plaque psoriasis · Psoriasic arthritis	Taltz®(2016)	Infections (especially of the upper respiratory tract), oropharyngeal pain, nausea.
	Brodalumab	· Common psoriasis	Kyntheum®(2017)	Flu, ringworm, headache, neutropenia, oropharyngeal pain, diarrhea, nausea, arthralgia.
ANTI-IgE	Omalizumab	· Asthma · Urticaria idiopática crónica	Xolair®(2009)	Headache, abdominal pain, pyrexia, parasitic helminth infections
ANTI-IL-5	Mepolizumab	· Eosinophilic asthma	Nucala®(2015)	Infections of the lower respiratory tract, infection of the urinary tract, headache, back pain, abdominal pain.
	Reslizumab	· Eosinophilic asthma	Cinqaero®(2016)	CPK elevation in blood
	Benralizumab	· Severe eosinophilic asthma	Fasenra®(2018)	Infections (especially, bacterial, viral and streptococcal pharyngitis), headache, fever, and hypersensitivity reactions.
ANTI-IL-6	Tocilizumab	· Rheumatoid arthritis · Juvenile rheumatoid arthritis · Cytokine release syndrome	Roactembra®(2009)	Infections, reactivation of tuberculosis, intestinal perforation, hypersensitivity reactions, neutropenia, hyperlipidemia.
	Sarilumab	· Rheumatoid arthritis	Kevzara®(2017)	
	Siltuximab	· Multicenter Castleman's disease	Sylvant®(2014)	
ANTI-IL-1	Anakinra	· Rheumatoid arthritis	Kineret®(2015)	Allergic reactions, liver enzyme elevation, infections, neutropenia, lung disorders.
	Canakinumab	· Periodic fever syndrome · Cryopyrin-associated periodic syndromes · Tumour necrosis factor receptor associated periodic syndrome · Hyperimmunoglobulin D syndrome · Mevalonate kinase deficiency · Familial Mediterranean fever · Still disease · Gouty arthritis	Ilaris®(2017)	Respiratory tract infections (pneumonia, bronchitis, flu-like symptoms, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infections), ear infection, cellulitis, gastroenteritis, urinary tract infection, vulvo-vaginal candidiasis, neutropenia.
ANTI-CD-28	Abatacept	· Rheumatoid arthritis · Psoriasic arthritis · Juvenile idiopathic arthritis	Orencia®(2007)	Infections, reactivation of tuberculosis, leukocytopenia.
ANTI-IL-4	Dupilumab	· Atopic dermatitis · Asthma · Chronic rhinosinusitis with nasal polyposis	Dupixent®(2017)	Conjunctivitis, oral herpes, eosinophilia, headache, allergic conjunctivitis, ocular itching and blepharitis
ANTI-IgG-1	Belimumab	· Systemic lupus erythematosus	Benlysta®(2011)	Bacterial infections, bronchitis, urinary tract infections, viral gastroenteritis, pharyngitis, nasopharyngitis, leukopenia, depression, migraine, diarrhea, nausea, limb pain.

The decision on whether to perform tuberculosis screening must be based on risk factors such as origin of the patient, occupation, previous immunosuppressive therapies and comorbidities such as diabetes or chronic kidney disease. During anti-TNF-α therapy, it is recommended to repeat screening on a yearly basis only in patients with risk factors[5].

The Consensus of the Spanish Society of Rheumatology recommends that latent tuberculosis is treated in the following settings: a) recent contact with a patient with a confirmed diagnosis of tuberculosis; b) history of partially-treated tuberculosis; c) positive Mantoux test; or d) residual lesions on chest X-ray[1].

In the protocol designed by the Rheumatology Service and the Hospital Pharmacy Service of Complejo Hospitalario of Navarra[31], it is recommended to prepare a medical record on risk contacts and perform a Mantoux test. In the case of a negative result, the test will be repeated or a blood test will be done (Quantiferon®). Given the high incidence of false negative results in these tests in patients receiving a steroid therapy, a chest X-ray is also recommended to exclude lesions suggestive of active infection.

In patients who have developed tuberculosisas as a side effect of anti-TNF-α therapy, immunosuppressive therapy can be resumed after anti-tuberculosis treatment has been completed[15].

Anti-TNF-α therapies: adalimumab, golimumab, certolizumab pegol and etanercept

These therapies are linked to a higher risk of tuberculosis[33-35]. Systematic reviews show a 4-fold increase in the rate of tuberculosis compared with patients not exposed to this agent[30].

Anti-interleukin-12/23: ustekinumab

The use of ustekinumab is not associated with a higher risk of tuberculosis in the global registry of patients with rheumatoid arthritis. However, screening for latent tuberculosis was performed and treatment was administered in all clinical trials[30] .

Anti-interleukin-17: secukinumab, ixekizumab and brodalumab

In vitro studies provide evidence of a lack of effect of secukinumab on Mycobacterum tuberculosis dormancy in granulomas[7].

A study of secukinumab with data from 21 clinical trials with different doses and indications, added to post-marketing data did not show any case of tuberculosis reactivation36. No cases of active tuberculosis have been reported either in relation to secukinumab, ixekizumab or brodalumab.

Over the last few years, several safety studies have demonstrated that tuberculosis is not linked to agents with this mechanism of action[13,36–38].

Anti-interleukin-6: tocilizumab, sarilumab and siltuximab

Inconsistent results have been obtained on tocilizumab. On the one hand, no cases have been documented of tuberculosis reactivation, although screening was not performed and patients with tuberculosis were not excluded in most of the clinical trials[15]. On the other hand, cases of tuberculosis have been reported in post-marketing studies.

An analysis of data about tocilizumab yielded an incidence of tuberculosis of 93 cases in 100,000 patients/year, although all cases were reported in regions with an intermediate-high prevalence of tuberculosis[7].

Some post-marketing studies suggest that the risk is similar to that observed with anti-TNF-α therapies and show a higher incidence of infection by other mycobacteriaand pneumonia caused by *Pneumocistis jiroveci*[30,39].

Anti-interleukin-1: anakinra and canakinumab

IL-1 is produced in lung granulomas of patients with active pulmonary tuberculosis. Some animal models suggest that anti-IL-1 therapies increase susceptibility to tuberculosis. Some polymorphisms of the IL-1B gene may influence the risk of extrapulmonary tuberculosis[7].

Only a few cases of tuberculosis have been documented in clinical trials, and although there are reports of tuberculosis reactivation, data from clinical trials and national registries do not show an increase in the risk of tuberculosis[7,30].

Anti-CD28 human monoclonal antibody: abatacept

The rate of tuberculosis in patients receiving abatacept seems to be lower than that in patients receiving TNF-α antagonists. In all clinical trials, including a total sample of 4,149 patients, only 8 cases of tuberculosis were recorded, which equates to an incidence rate of 0.07 [0.03 to 0.13] in 100 patients-year[27].

Other mechanisms

No cases have been reported to date of active tuberculosis reactivation with guselkumab[9] or dupilumab[21].

Anti-IgE (omalizumab) or anti-cytokines Th2 (dupilumab, mepolizumab...) are unlikely to augment the risk of tuberculosis, as an increase in Th2 could negatively affect response in tuberculosis control. Indeed, no relationship has been observed between the use of these agents and a higher risk for tuberculosis. However, tuberculosis screening was not performed in clinical trials or post-marketing studies[30].

In summary

Prior to anti-TNF- therapyα

Perform screening in all patients before an anti-TNF-α. is started

In patients with:
- History of partial treatment for tuberculosis.
- Positive Mantoux test*.
- Radiographic lesions suggestive of latent infection.
- Recent contact with a patient with tuberculosis.

Start isoniazid 300 mg/day or 900 mg twice weekly for 6 (65% effectiveness) to 12 months (75% effectiveness)[31]. Complete treatment with isoniazid before biological therapy is started. Initiate biological therapy 1-2 months after tuberculostatic treatment has been completed[30,40].

In case of previous history of tuberculosis, perform a monthly screening test during the first 3 months.

Perform a regular monitoring of patients with radiographic findings consistent with healed tuberculosis or evidence of a healed extrapulmonary tuberculosis.

Treat active tuberculosis for at least 2 months before starting an anti-TNF-α therapy[40].

During treatment with an anti-TNF-α agent

If a patient develops tuberculosis during treatment with a biological agent, consider suspending the anti-TNF-α agent at least until anti-tuberculosis treatment is initiated, preferably until anti-tuberculosis therapy is completed. If possible, resume anti-TNF-α therapy 1-2 months after anti-tuberculosis therapy has been completed.

If biological therapy is suspended to treat tuberculosis, be aware that the patient may develop a hyperinflammatory response at 4-20 weeks after discontinuation, which improves with steroids or when anti-TNF-α is resumed[30].

Tuberculosis screening reduces the risk of reactivation of latent tuberculosis by up to 7 times

With other agents

Tuberculosis screening is recommended in the SmPCs of secukinumab[4], ixekizumab[43], abatacept[26], anakinra[44], ustekinumab[45], tocilizumab[17], sarilumab[46], canakinumab[47] and guselkumab[11] before treatment is initiated.

For the moment, it seems reasonable to apply the recommendations for anti-TNF-α therapy to the other therapies described[30,4].

Herpes zoster

It is one of the most frequent adverse effects of anti-TNF-α therapies4. There is an increased risk of herpes zoster infection in patients with autoimmune inflammatory diseases[49-51]. Patients with rheumatoid arthritis are estimated to have a 65-90% higher risk of herpes zoster infection than the general population50. However, the risk is lower in patients with psoriasis or psoriatic arthritis, and not comparable with rheumatoid arthritis[9].

A review of 41 studies revealed that the risk of herpes zoster infection increased when biologicals were combined with other disease-modifying therapies but not when used in monotherapy. There is no conclusive evidence that allows to determine the risk associated with IL 12/23, 17 and 23 or apremilast[4].

In the anti-TNF-α (etanercept, infliximab, adalimumab and certolizumab-pegol) group of a cohort study (n=19,282), the most frequent opportunistic infection was herpes zoster, with an incidence of 51 cases/100,000 patient-years, followed by *Pneumocystis jiroveci* and *Legionela spp*[35]. Different studies have demonstrated that anti-TNF-α therapies double the risk for herpes zoster infection[52,5].

(*) The tuberculin sensitivity test (Mantoux) is not useful in immunosuppressed patients with normal X-ray results. A risk/benefit analysis must be performed on a case-by-case basis. Provided that the treatment is not contraindicated, it is recommended that latent tuberculosis is treated. Chronic hepatitis, peripheral neuropathy (preventable with pyridoxine), regular and abusive use of alcohol, pregnancy or previous tuberculosis infection are not contraindications to isoniazid[41].

In a study, herpes infections were found to be more frequent in the etanercept group compared with the secukinumab group, with a similar incidence of herpes zoster infection[13].

In a retrospective analysis, the incidence of herpes zoster infection was 2.5% during the first year of treatment with ustekinumab. Cases of meningitis and zoster varicella virus infection were also reported. Two cases of herpes zoster infections were reported in patients treated with mepolizumab in two different clinical trials and in a systematic review that included seven clinical trials. Varicella-zoster virus infection has also been associated with the use of anakinra and canakinumab. Inconsistent results have been obtained in relation to the risk linked to belimumab, with some placebo-controlled clinical trials showing a higher incidence (6.2% *vs* 5.1%), whereas others show a lower incidence[25].

In summary

Although a recent review does not provide evidence of an association of abatacept and tocilizumab with a higher risk of herpes zoster infection[5], it is included as a frequent adverse event in the SmPC.

There is controversy as to the causal relationship with these therapies, as these patients are at an increased risk of herpes zoster infection secondary to their underlying disease.

HBV and HCV reactivation

Cases of HBV reactivation and fatal liver failure have been documented[1,5]. However, other patients with HBV do not show liver dysfunction or their viral load even decreased during anti-TNF-α therapy.

No episodes of HBV reactivation were observed in patients receiving ustekinumab who were HBsAg-positive or at risk of hidden HBV infection (HBsAg negative, anti-Core positive antibodies) who received prophylaxis. In contrast, there are reports of reactivation in HBsAg-positive patients who did not receive prophylaxis (2 in 7). HCV and hepatocellular carcinoma reactivation were observed in a patient with HCV, cirrhosis and treated hepatocellular carcinoma during ustekinumab therapy. Screening is recommended[5].

Most of the information available on the use of biologicals in HCV patients is based on anti-TNF-α therapies. Only a few cases have been documented of HCV exacerbation during anti-TNF-α therapy, with a good clinical response to concomitant treatment with etanercept and antivirals for HCV 15. In a systematic review of data from 153 HCV-positive patients who received anti-TNF-α therapy, there was a confirmed case and five suspected cases of exacerbation of HCV infection[5].

Live attenuated vaccines are contraindicated during biological treatment

In the presence of latent HCV infection, it is recommended that administering an anti-TNF-α therapy be considered. Liver function and viremia must be monitored if antiviral treatment is not administered[15].

The information available on tocilizumab and hepatitis comes from case series studies. There are two case reports of patients with treated HBV and the case of a patient with HCV who showed a good response to treatment with tocilizumab. In addition, small case series report that 2 in 25 patients previously exposed to HBV exhibited sustained viremia during treatment with tocilizumab[7]. In Japan, post-marketing reports of 52 patients previously exposed to HBV (serologic status is unknown) do not document cases of hepatobiliary disorders secondary to HBV or HCV reactivation[7].

No cases have been observed either of HBV and HCV reactivation in patients receiving anti-IL-17 therapies (screening was also performed in most of the clinical trials)[5].

There is no consensus on the use of abatacept in patients with HBV or HCV. There are cases of latent HBV infection generally associated with prophylactic treatment, or with HCV that did not show significant liver function deterioration[27]. It is recommended to perform a risk/benefit analysis and close monitoring of the liver function and viral load of patients with HBV or HCV treated with abatacept.

In summary

It is recommended to perform serology and HBV tests[7].

HCV screening is recommended. In the presence of a positive result, consider the option of administering an antiviral treatment based on the risk of reactivation. In case of latent infection, it is recommended to use an anti-TNF-α therapy. Liver function and viremia must be monitored if antiviral treatment is not administered[15,5].

HBsAg-positive patients should receive prophylaxis before the start of immunosuppressive therapy. Prophylaxis with lamivudine 100mg/day has been associated with favourable short-term clinical outcomes[15].

Immunisation is recommended in HBsAg-negative patients before the biological therapy is initiated[5,15].

Vaccines

It is important that an immunisation programme is established before immunomodulatory therapy with biologicals is started.

In general terms, vaccines composed of live attenuated microorganisms are contraindicated, as they are linked to a high risk of infection due to the level of immunosuppression induced by the biological agents[1]. However, further studies are needed to confirm this statement, as some observational studies suggest a safer profile than expected[5].

Although the administration of inactive vaccines is not contraindicated, response may be reduced during treatment with biological disease-modifying therapies[5]. The labels of dupilumab and canakinumab indicate that response to inactive vaccines is not affected by the therapy[20,47].

Influenza vaccine

Some studies demonstrate an increase in the incidence of influenza in patients with rheumatoid arthritis[5,51]. The incidence of influenza complications in these patients is also higher, especially in patients with an age ≥70 years. Anti-TNF-α therapies are independently associated with a higher probability of developing symptoms of influenza [OR (95% CI):2.4 (1.2 to 4.8)[59].

Except for rituximab, and probably abatacept, it seems that other biologicals do not affect immunologic response to influenza vaccine[5].

It is recommended that influenza vaccine is administered to all patients who are starting an immunosuppressive biological therapy.

Pneumococcal vaccines

Patients with rheumatoid arthritis and systemic lupus erythematosus are at a higher risk for pneumonia caused by invasive pneumococcal infection, especially young patients (18-to-49 years)[5].

A lower volume of antibodies was observed after PCV-13 immunization in 22 patients with rheumatoid arthritis treated with etanercept alone or in combination with methotrexates compared with patients not receiving a biological treatment or methotrexate. Nevertheless, the vaccine was proven to be effective and safe in these patients[5].

Pneumococcal immunization is recommended in all patients who are starting an immunosuppressive biological therapy.

Human papillomavirus vaccine

Genital human papillomavirus (high-risk subtypes included) and squamous intraepithelial lesions are more prevalent in women with systemic lupus erythematosus. Therefore, annual cytology is recommended in immunosuppressed women older than 21 years[31].

In patients with rheumatoid arthritis or systemic sclerosis, the prevalence of the human papillomavirus (HPV) is similar to that observed in the general population[5]. Due to immunosuppression, patients with rheumatoid arthritis must be vaccinated when they meet the indication[58,60].

Varicella zoster virus vaccine

Zostavax® vaccine (attenuated microorganisms) is contraindicated in immunosuppressed patients[6]. On the other hand, patients receiving an immunosuppressive treatment (steroid therapy included) for malignant solid tumors or severe chronic diseases (chronic renal insufficiency, autoimmune diseases, collagenosis, severe bronchial asthma) are predisposed to develop severe varicella.

A recent review supports the administration of a recombinant vaccine to all patients with psoriasis or psoriatic arthritis receiving tofacitinib, corticosteroids or a combination therapy. In other cases, immunization must be considered on an individual basis[4].

US Centers for Disease Control and Prevention recommend varicella immunization in patients on biologicals. The vaccine must be administered at least 1 month after completion of biological therapy or 2-4 weeks before the start of the biological therapy[5].

Hepatitis B virus vaccine

The prevalence of HBV in the population with rheumatic autoimmune diseases seems to be similar to that in the general population. Indeed, a lower prevalence has been observed in some studies[5].

It is recommended to perform a HBV serology test and analyse the HBV surface antigen (HBsAg) and the HBsAg antibody (Anti-HBs). The hepatitis B vaccine is effective in most patients with an inflammatory autoimmune

disease. In HBsAg-negative patients, it is recommended that the vaccine be administered before the start of the therapy[15,5].

Other vaccines

Hepatitis A and poliomyelitis (inactivated viruses) or meningococcus C and *Haemophilus influenzae* B (conjugated) are not contraindicated because they are not composed of live microorganisms. However, they are not expressly indicated in patients receiving biologicals. The administration of these vaccines must be considered on a case-by-case basis.

Immunization is recommended in HBsAg-negative patients prior to initiation of a biological therapy

Cancer

In patients with a history of solid cancer, consider the risk of relapse, since patients with rheumatoid arthritis seem to be at a higher risk for basal cell carcinoma1. A recent systematic review of placebo-controlled studies associated anti-interleukin therapies with a higher risk of cancer in patients with different rheumatic diseases [OR (95% CI): 1.52 (1.05 to 2.19)][4].

There is controversy about the risk of developing lymphoproliferative disease in patients with rheumatoid arthritis treated with anti-TNF-α therapies. No association has been found in ankylosing spondylitis. For the moment, the use of anti-TNF-α therapies in patients with lymphoproliferative disease is not recommended[1].

Other risks

TNF-α antagonists and tocilizumab have been associated with optic neuritis, multiple sclerosis and other demyelinating disorders. Suspend treatment in case of occurrence[1].

Considering the half-life and immunosuppressive effect of biologicals, the Spanish Society of Rheumatology recommends to suspend biological therapies prior to elective major surgery. In general, in the absence of complications, biological therapy can be resumed at 10-14 days[1].

HIV screening is recommended in high-risk patients. Only administer biologicals to patients with stable HIV, >200/mL CD4 due to the risk of reactivation if the viral load is not controlled[5,15].

There are no data or recommendations on the use of recently-approved biologicals in pregnant and breastfeeding women: sarilumab, ustekinumab, ixekizumab, secukinumab, belimumab; ni tampoco para apremilast.

The first alternative during pregnancy and breastfeeding is certolizumab followed by adalimumab[31].

Pregnancy during treatment must be avoided.

Suspected Adverse Drug Reactions (ADR) reported by the Pharmacovigilance System of Navarra

The data presented correspond to suspected adverse drug reactions reported in Spain from January 2000 to February 2020 related to the following drugs:

- Anti-TNF-α: golimumab, etanercept, adalimumab, certolizumab.
- Anti-IL: ustekinumab, tocilizumab, secukinumab, sarilumab, ixekizumab, guselkumab, canakinumab, brodalumab, anakinra, dupilumab.
- R03DX group (other systemic drugs for asthma): omalizumab; mepolizumab; reslizumab; benralizumab.
- Selective immunosuppressors: belimumab and abatacept.

The data provided on the number of reported cases cannot be used to calculate the frequency of occurrence of adverse reactions in patients using the drug or allow to establish a causal relation or compare safety among different drugs. Nevertheless, these data can be used as a starting point to develop hypotheses.

Healthcare professionals should not select a therapy based on this information (Table 4).

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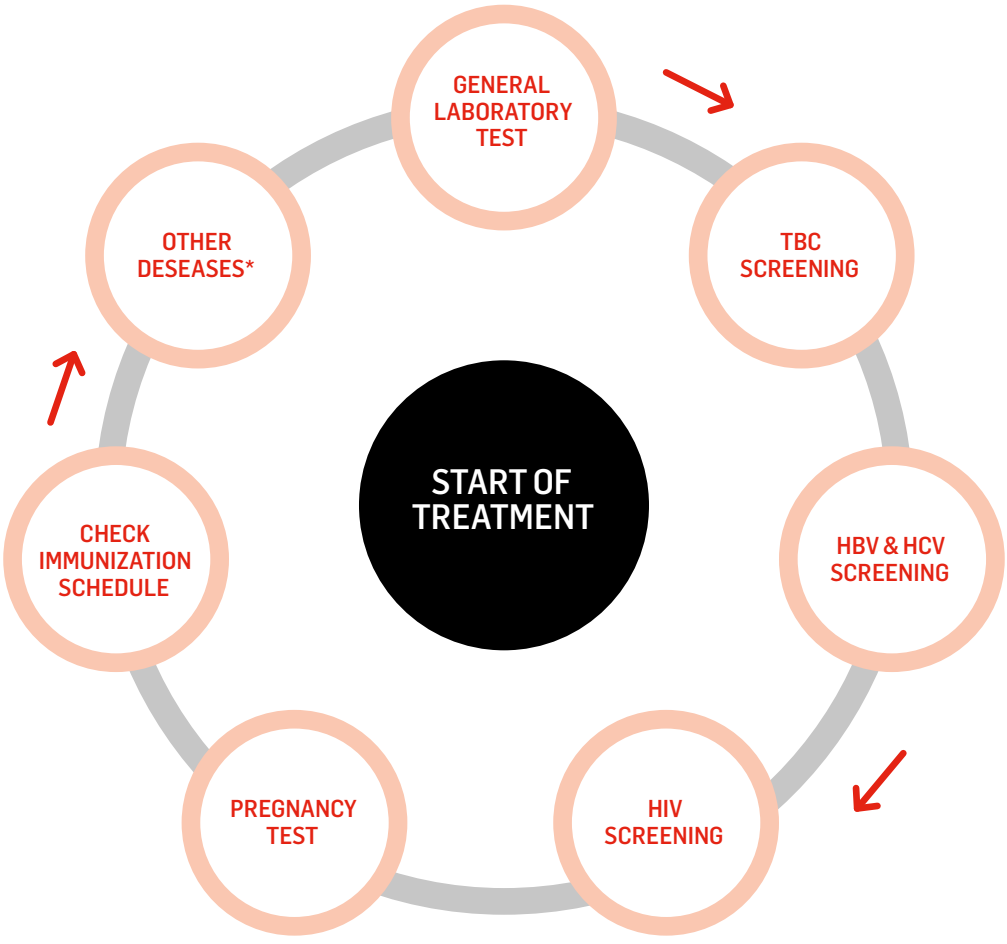
Table 2. Immunization recommendations in patients receiving a biological treatment.

VACCINE	MICROBIOLOGICAL CLASSIFICATION	RECOMMENDATION
Influenza	Fractionated microorganisms	Recommended
	Subunits	
Pneumococcus	Simple polysaccharids	Recommended
	Conjugated	
Hepatitis B	Recombinant	Recommended in seronegative patients
Human Papilloma Virus	Recombinant	Possible
Hepatitis A	Inactivated	Possible
Poliomyelitis	Inactivated	Possible
Meningococus C	Conjugated	Possible
Haemophilus influenzae B	Conjugated	Possible
Varicella	Attenuated	Contraindicated
Parotiditis / Rubeola / Measles	Attenuated	Contraindicated
Yellow Fever	Attenuated	Contraindicated
Typhoid Fever	Attenuated	Contraindicated

Figure 1. Factors to be considered before the start of biological therapy.



(*) Assess thoroughly each case of heart failure, cytopenias, interstitial lung disease, demyelinating disease, or tumor disease.

Table 3. Summary of the available evidence on the risk of infections associated with biological agents.

Drug	Increased risk of infections	Tuberculosis risk / screening	Herpes zoster risk	HBV risk	Observations and recommendations
Anti-TNF-α Adalimumab Etanercept Infliximab Certolizumab Golimumab	Moderate/ elevated	• Clear evidence of an increased risk both, in vitro and in clinical practice. • Screening: YES	Yes	Yes	• Test for chronic HBV infection before starting the therapy. • Antiviral prophylaxis in HbsAg-positive patients while on treatment. • Monitor HBV viral load in anti-HBc-positive patients, HbsAg-negative patients to detect an eventual reactivation of hidden HBV infection. • Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary). • Adequate antiviral immunization according to the age of the patient.
Anti-IL-6 Tocilizumab Sarilumab Siltuximab	Moderate	• Risk similar to that of anti-TNF-α. • Screening: YES	Controve	Yes	
Anti-IL-12 y 23 Ustekinumab	Low	• No increased risk has been observed, although screening is recommended in all clinical trials. • Screening: YES	Yes	Yes	• No apparent increased risk of infection. • Test for chronic HBV infection before starting the therapy (followed of antiviral prophylaxis in HbsAg-positive patients). • Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary) due to the theoretical risk of active tuberculosis. • Appropriate antiviral immunization according to the age of the patient.
Anti-IL-12 y 23 Guselkumab Tildrakizumab	Insufficient evidence	• No reported cases • Screening: YES	Insufficient evidence	No	• Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary) due to the theoretical risk of active tuberculosis. • Before the start tildrakizumab therapy, consider the administration of all appropriate vaccines according to current immunization guidelines. If ha patient has received a live virus or bacteria, it is recommended to wait 4 weeks before tildrakizumab therapy is started. Patients treated with Ilumetri® should not receive live vaccines during the treatment or during the first 17 weeks after treatment completion.
Anti-IL-17 Secukinumab Ixekizumab Brodalumab	Low. Higher risk of *Candida spp*	• No cases have been observed of active tuberculosis infection. • Screening: YES	Low	No	• Slight increase in the risk of mild-to-moderate infection. • Increased risk of mild-to-moderate mucocutaneous candidiasis (slightly higher in ixekizumab than in secukinumab). • Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary).
Anti-IL-5 Mepolizumab Reslizumab Benralizumab	Low	• It apparently does not increase the risk of tuberculosis. • Screening: YES	Few cases with mepolizumab. Some authors recommend considering immunization.	No	• Test for latent or active helminth infections. If patients get infected while on mepolizumab/benralizumab and do not respond to antiihelminthic therapy, consider suspending the treatment temporarily.
Anti-IL-1 Anakinra Canakinumab	Moderate/ elevated	• Theoretical risk, studies performed in regions with a low prevalence. • Screening: YES	Low	No	• Moderate increase in the risk of mild/moderate infection in children and adults with autoinflammatory or autoimmune diseases. • Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary). • Therapy must be suspended progressively, as abrupt withdrawal may induce a seizure of the underlying auto-inflammatory disease. • Appropriate antiviral immunization according to the age of the patient.
Anti-Ig E Omalizumab	Increase of parasite infections. Screening is recommended according to the origin of the patient.	• Theoretically, it does not affect. • An increased risk has not been observed, although screening is not necessary • Screening: NO	No	No	• Caution with patients at risk of helminth infection.
Anti-CD-28 Abatacept	Low	• Screening: Si	Controve	Controve	• Test for latent tuberculosis before starting the therapy (followed of the adequate treatment, if necessary).
Anti-IL-4 Dupilumab	Insufficient evidence	• It does not seem to affect • Screening: NO	No	Insufficient evidence	• Caution with patients at risk of helminth infection .
Anti-IgG1 Belimumab	Insufficient evidence	• Risk unknown. • Screening: NO	Yes	Insufficient evidence	

Table 4. Suspected adverse drug reactions reported in Spain from January 2000 to February 2020.

Main diseases	Anti-TNF α	Anti-IL	R03DX	Belimumab	Abatacept
Tuberculosis	389	1			1
Herpes zoster virus	81	11	1	1	4
Hepatitis B reactivation	14	1			

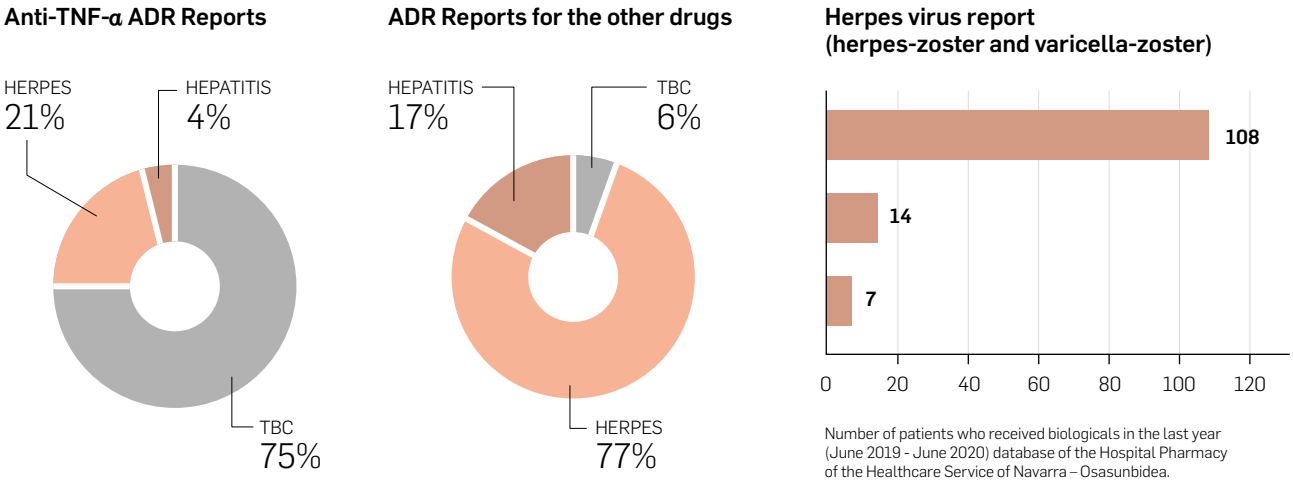
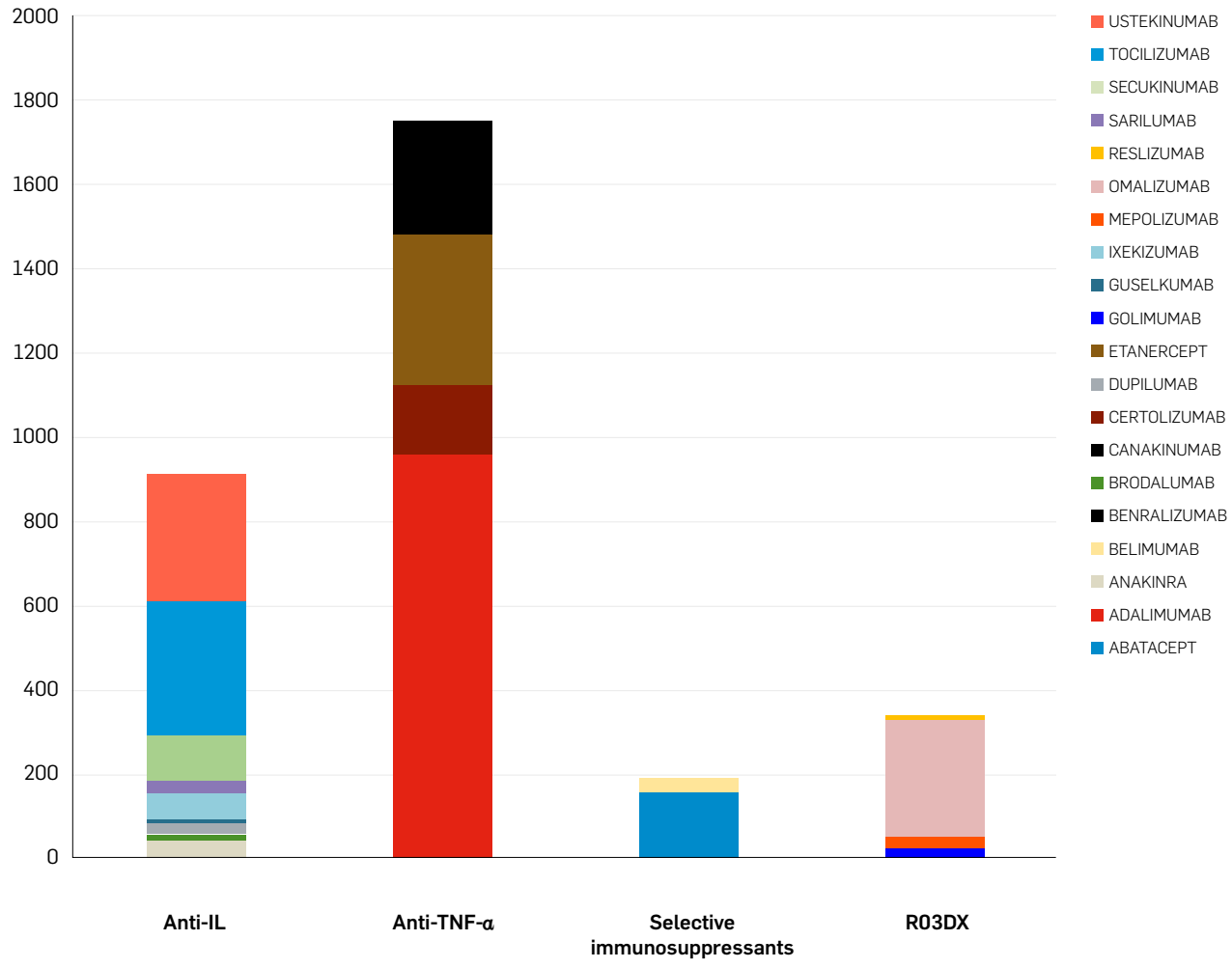


Figure 2. Number of patients who received biologicals in the last year (June 2019-June 2020). Database of the Hospital Pharmacy of the Healthcare Service Of Navarra—Osasunbidea.



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