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# INFECTION RISK OF TARGETED SYNTHETIC DRUGS USED IN IMMUNE-MEDIATED INFLAMMATORY DISEASES

OBJECTIVE To review the available evidence concerning the infectious risks related to the targeted synthetic drugs used in immune-mediated inflammatory diseases and the measures for preventing infections in this type of disease. MATERIAL AND METHODS Targeted synthetic drugs with an indication in immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, inflammatory bowel disease, psoriasis and atopic dermatitis, were selected. The summary of product information for these drugs were consulted and a search carried out in Pubmed, reviewing the most relevant articles and clinical guidelines. RESULTS AND CONCLUSIONS Patients with immune-mediated inflammatory diseases present a higher risk of developing infections compared with the general population, partly due to immunosuppressive therapy. The infection risk associated with these treatments depends on the mechanism of action. There is no evidence for an increased risk of serious infections associated with apremilast use. Therefore, prior to initiating therapy with apremilast, no type of test other than clinical monitoring of the disease needs to be performed. Treatment with JAK inhibitors has been associated with an increase in infection risk, including reactivation of tuberculosis, herpes zoster and hepatitis B, among other infections. The vaccination status must be evaluated, a screening for infection with hepatitis B or latent tuberculosis performed, and an active systemic or local infection ruled out before starting treatment with JAK inhibitors. The inactivated vaccines recommended for patients being treated with JAK inhibitors are pneumococcus, influenza, hepatitis A, hepatitis B, herpes zoster and SARS-CoV-2. Attenuated live vaccines are contraindicated in these patients. Insufficient data are available to demonstrate that apremilast or JAK inhibitors increase the risk of COVID-19 infection and its complications. It is important that both healthcare professionals and patients are aware of the infection-prevention measures and recognise the signs and symptoms of infection before and during treatment with these drugs. KEY WORDS Targeted synthetic drugs, immune-mediated diseases, infection risk, herpes zoster, tuberculosis, vaccination

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## Introduction

Patients with immune-mediated inflammatory diseases present a higher incidence and severity of infectious diseases than the general population[1]. This higher risk of infection is associated with the advanced age, the type of disease and its degree of activity, the comorbidities and the concomitant inmunosuppresive treatment.[2]

Disease-modifying drugs (DMARDs) are intended to slow disease progression and to improve patients' symptoms and quality of life. Depending on their size manufacturing method, they are classified as synthetic DMARDs (small molecules obtained by chemical synthesis) and biological DMARDs (larger molecules obtained using biotechnology). The first to be incorporated into the therapeutic arsenal were conventional synthetic DMARDs, although it is not clear if they act against specific targets. DMARDs aimed at specific targets, both synthetic and biological, were then incorporated.[3]

The inhibition of specific targets induces an anti-inflammatory response that is responsible for the therapeutic effect, although it may also affect the response to acute infections and the control of latent or chronic infections. It is important that both healthcare professionals and patients are aware of the infection-prevention measures and recognise the signs and symptoms of infection before and during treatment with these drugs.[4]

In this bulletin we will focus on describing the infection risks of synthetic targeted DMARDs used to treat immune-mediated inflammatory diseases, namely phosphodiesterase-4 (PDE4) inhibitors and Janus kinase (JAK) inhibitors. We will review the evidence available concerning the infection risks related to these drugs and the infection-prevention measures for these type of diseases. The infection risks of biological DMARDs have been discussed previously.[5]

## Phosphodiesterase-4 (PDE4) inhibitor: apremilast

### Infection risks

Apremilast was approved by the European Commission (EC) in 2015 and is authorised for the treatment of psoriatic arthritis, plaque psoriasis and Behçet's disease. This PDE4 inhibitor results in a decrease in the inflammatory response by modulating the expression of inflammatory cytokines such as tumour necrosis factor (TNF), interleukin 23 and 17 (IL-23 and IL-17) and anti-inflammatory cytokines such as interleukin 10 (IL-10). All the above are involved in psoriatic arthritis and psoriasis. Apremilast has been shown to be effective for the treatment of these conditions, although it may increase the risk of infections.[6]

***Patients with immune-mediated inflammatory diseases present a higher risk of developing infections***

Its summary of product information describes upper respiratory tract infections as very common (≥1/10) and nasopharyngitis and bronchitis as common adverse reactions (≥1/100 to <1/10). In addition, serious infections, including opportunistic infections and transmission of infections through live attenuated vaccines, are included as important potential risks in the risk management plan for apremilast from the European Medicines Agency (EMA), which was updated in May 2022.[7,8]

The incidence of non-opportunistic systemic infections in clinical trials with psoriatic arthritis was 0.3%, 0.4% and 0.6% for placebo, apremilast 20 mg/12 hours and apremilast 30 mg/12 hours, respectively. The corresponding values in clinical trials with psoriasis were 0.5% and 0.9% for placebo and apremilast 30 mg/12 hours, respectively, and in the clinical trial with Behçet's disease, the values were 1.9% and 0% for placebo and apremilast 30 mg/12 hours during the first 12 weeks of treatment phase, with two cases of severe infection being reported in the subsequent, open-label treatment phase with apremilast.[8,9]

The incidence of opportunistic systemic infections in clinical trials with psoriatic arthritis and plaque psoriasis was low (≤0.1% for apremilast). No case of active tuberculosis, herpes zoster, reactivation of latent tuberculosis or of hepatitis C was reported. However, in some trials, patients with a history of tuberculosis or hepatitis C antibodies were excluded.[8,9]

The data available in the EMA risk management plan show that the incidence of infections did not increase when patients continued with long-term apremilast treatment.[8]

In a post-marketing safety study carried out in a US cohort and funded by the laboratory, the reactivation rate for herpes zoster, hepatitis C or tuberculosis was found to be lower in patients treated with apremilast than in those receiving biological DMARDs and conventional DMARDs used in psoriatic arthritis or psoriasis. However, care must be taken when interpreting these data because outcomes assessed are relatively rare events.[10]

Other important risks to consider include suicidal ideation and behaviour, depression, anxiety, agitation, vasculitis, malignant neoplasms, serious cardiovascular events (cardiovascular death, myocardial infarction and non-fatal stroke), miscarriage and delayed foetal development in pregnant women.[8]

***Tuberculosis screening is not required prior to apremilast treatment***

## Prior evaluation and follow-up

### Before starting treatment with apremilast

There is no need to perform any type of additional test other than clinical monitoring of the disease.

### During treatment with apremilast

Special attention must be paid to patients exhibiting symptoms such as mood alterations, weight loss or serious cardiovascular events.[7,8]

## Janus kinase inhibitors (JAK): ▼Tofacitinib, ▼Baricitinib, ▼Upadacitinib, ▼Filgotinib, ▼Abrocitinib

### Infection risks

JAKs are a family of tyrosine kinases linked to numerous intracellular cytokine receptors that are found as four isoforms (JAK1, JAK2, JAK3 and TYK2). They are intracellular signal transduction molecules that translate the effects of some cytokines and growth factors into cellular responses. These mediators are important for the immune defence and in immune-mediated inflammatory diseases.

The JAK inhibitors available differ in their selectivity for specific JAK isoforms. Thus, tofacitinib is considered to be a pan-JAK inhibitor, baricitinib inhibits JAK1 and JAK2 with greater selectivity, upadacitinib preferably inhibit JAK 1 and the JAK1/3 pair, and filgotinib and abrocitinib are highly selective JAK1 inhibitors. However, this difference in selectivity is not obviously related to their safety and efficacy profile in clinical practice.[11–14]

#### ▼Tofacitinib

Tofacitinib was approved by the EC in 2017 and is authorised for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and ulcerative colitis.

Its summary of product information describes pneumonia, influenza, herpes zoster and urinary tract infection as common (≥1/100 and < 1/10), and tuberculosis, diverticulitis, pyelonephritis, cellulitis, herpes simplex, viral gastroenteritis and viral infection as uncommon adverse reactions (≥1/1000 to <1/100).

The infections described as rare (≥1/10,000 to <1/1000) are sepsis, disseminated tuberculosis, necrotizing fascitis, bacteriaemia, staphylococcus bacteriaemia, Pneumocystis jirovecii pneumonia, pneumococcal pneumonia, bacterial pneumonia, encephalitis, atypical mycobacterial infection, cytomegalovirus infection and arthritis.

The infections described as very rare (<1/10,000) are tuberculosis of the central nervous system, cryptococcal meningitis and Mycobacterium avium complex infection.[11]

The risk factors related with serious infections were tofacitinib dose, elderly age, male sex, confirmed lymphopaenia at -baseline (<1000 cells/µL), treatment with other immunosuppressants (including corticosteroids), history of diabetes mellitus, chronic obstructive pulmonary disease, high body mass index and patients from certain Asian countries.[15]

The risk of herpes zoster reactivation in patients treated with tofacitinib appears to be dose-dependent and increased in Japanese and Korean patients and those with long-term disease who have received two or more biological DMARDs. The risk of herpes zoster infection is increased in patients with absolute lymphocyte counts <1000 cells/µL. The risk of reactivation chronic viral hepatitis is unknown.[16]

Other important risks to consider include venous thromboembolism (deep vein thrombosis and pulmonary embolism), myelotoxicity, anaemia, hyperlipidaemia, serious cardiovascular events, malignant neoplasms, interstitial lung disease and gastrointestinal perforation, amongst others.[16]

#### ▼Baricitinib

Baricitinib was approved by the EC in 2017 and is authorised for the treatment of rheumatoid arthritis and atopic dermatitis.

The infections described in the summary of product information as very common adverse reactions (≥1/10) are upper respiratory tract infections, and as common adverse reactions (≥1/100 to < 1/10) are herpes zoster, herpes simplex, gastroenteritis, urinary tract infection and pneumonia.[12]

Herpes zoster is a known risk of baricitinib treatment, and as such is included in the EMA risk management plan, which was updated in June 2022.17 However, 89% of cases reported were classified as non-serious. Only 8.5% of patients included in clinical trials with rheumatoid arthritis exhibited multidermal herpes zoster. In addition, only 5% of cases reported developed postherpetic neuralgia as a complication.

As with tofacitinib, the risk of herpes zoster reactivation was increased in Japanese population, elderly patients and patients with long-term disease who had received two or more biological DMARDs.

The risk factors associated with serious infections were elderly age, concomitant corticosteroid treatment, prior use of biological DMARDs, low body weight, overweight or obesity, and patients of Asian origin.

Other important risks to consider include venous thromboembolism (deep vein thrombosis and pulmonary embolism), myelotoxicity, hyperlipidaemia, malignant neoplasms and gastrointestinal perforation, among others.[17]

### ▼Upadacitinib

Upadacitinib was approved by the EC in 2019 and is authorised for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis.[13]

The infections described as very common adverse reactions (≥1/10) are upper respiratory tract infections. Herpes zoster, herpes simplex, bronchitis, folliculitis and influenza infections being classified as common (≥1/100 to < 1/10) and pneumonia, oral candidiasis and diverticulitis being classified as rare adverse reactions (≥1/1000 to <1/100).[13]

The risk factors for herpes zoster reactivation are similar to other JAK inhibitors discussed above.

The rate of tuberculosis was 1.8 events per 100 patients/year, which is higher than that reported for tofacitinib (all doses) and baricitinib (4 mg), namely 0.19 and 0.2 events per 100 patients/year, respectively.

Other important risks to consider include venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious cardiovascular events, malignant neoplasms and gastrointestinal perforation, among others.[18]

## *Treatment with JAK inhibitors increases the risk of serious and opportunistic infections*

### ▼Filgotinib

Filgotinib was approved by the EC in 2020 and is authorised for the treatment of rheumatoid arthritis and ulcerative colitis.[14]

The infections described as common adverse reactions (≥1/100 to < 1/10) are urinary tract infection and upper respiratory tract infection, with herpes zoster and pneumonia being described as rare (≥1/1000 to <1/100).[14]

Both serious and opportunistic infections, as well as the herpes zoster reactivation, are included in the EMA risk management plan for filgotinib[19], as is the case for other JAK inhibitors. However, in light of data from the pivotal clinical trials for filgotinib, the rate of serious infections and herpes zoster in the integrated summary of safety was lower than that published for biological DMARDs.[20]

Other important risks to consider include venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious cardiovascular events, malignant neoplasms, gastrointestinal perforation and teratogenicity, amongst others.[19]

### ▼Abrocitinib

Abrocitinib was approved by the EC in 2021 and is authorised for the treatment of moderate to severe atopic dermatitis in adults. At the time of drafting this bulletin, it was not marketed in Spain.

The summary of product information describes herpes simplex and herpes zoster infections as common adverse reactions (≥1/100 to <1/10) and pneumonia as rare (≥ 1/1000 to < 1/100). In clinical trials of abrocitinib versus placebo, infections were reported with higher frequency in patients treated with abrocitinib 100 mg and 200 mg (34.9% and 34.8%) vs placebo (27.4%).[21]

A safety analysis was performed with the integrated data from clinical trials of abrocitinib versus placebo (one phase IIb, four phase III and one extension trial). The proportion of patients with serious infections was similar between the abrocitinib 200 mg, abrocitinib 100 mg and placebo groups. The most common serious infections were herpes-related. No case of tuberculosis or other opportunistic infections was reported.[22]

An increase in the incidence rate of herpes zoster per 100 patients/year was observed in the abrocitinib 200 mg and 100 mg groups versus placebo (5.16 and 1.90 versus 0). A multivariate analysis showed a higher risk of herpes zoster with the abrocitinib 200 mg dose, age ≥65 years and serious atopic dermatitis at the start of treatment. As with other JAK inhibitors, these events were mostly mild or moderate in severity and resolved with oral antiviral treatment.[22]

In this analysis, an increase in the incidence rate of herpes simplex per 100 patients/year was observed in the abrocitinib 200 mg and 100 mg groups versus placebo (16.22 and 12.07 versus 7.20). However, the incidence rates for eczema herpeticum were similar in the abrocitinib 100 mg and placebo, with no cases being reported in the abrocitinib 200 mg group. The most significant risk factors for herpes simplex or eczema herpeticum were a history of herpes simplex or eczema herpeticum and serious atopic dermatitis at the start of treatment.[22]

## Prior evaluation and follow-up

### Before starting treatment with a JAK inhibitor

It is essential to assess a series of key aspects to reduce the risk of infections. Vaccination status and screening for latent infections at diagnosis will determine the preventive measures required.

A clinical interview should be conducted to capture the history of infections, as well as the risk of latent or active tuberculosis, hepatitis B immunisation status, history of disease and vaccination against measles, mumps, rubella and chickenpox. The history of past travel and future travel plans to regions with endemic infectious diseases should also be considered.

Signs of active systemic or local infection (gingivitis, oral or vaginal candidiasis) should be ruled out by a physical examination. Targeted synthetic drugs are contraindicated in patients presenting active tuberculosis and those with serious, active infections such as sepsis or opportunistic infections. To that end, it will be necessary to perform tuberculosis screening to detect latent tuberculosis. Care should be taken when treating patients with recurrent infections, with a history or opportunistic infections or serious infections, patients who live in, or have travelled to regions with endemic mycoses, or with concomitant conditions that predispose them to infections.

***Treatment with JAK inhibitors should not be started with an absolute lymphocyte count (ALC) of less than 750 cells/mm³, and should be discontinued with a count of less than 500 cells/mm³***

With regard to laboratory tests, a complete blood count should be requested. Treatment should not be started in patients with an absolute lymphocyte count (ALC) of less than 750 cells/mm$^3$, and treatment should be discontinued with a count of less than 500 cells/mm$^3$.

JAK inhibitors should not be administered in combination with biological DMARDs or powerful immunosuppressants, such as azathioprine or ciclosporin, as the immunosuppressive effect is enhanced and the infection risk increases.[11]

One requirement for starting treatment with JAK inhibitors is the prior use of a TNF inhibitor, unless this is contraindicated.[11]

Patients older than 65 years, smokers or ex-smokers and those presenting additional cardiovascular risk factors or for the development of neoplasms should not receive treatment with these drugs unless there is no therapeutic alternative available.

### During treatment with a JAK inhibitor

The following follow-up should be performed:

*Infection*

Patients should be monitored for the possible onset of signs and symptoms of infection during treatment with a JAK inhibitor. In case of clinically important active viral or bacterial infections, JAK inhibitors should not be used until antibiotic or antiviral treatment, as applicable, has been completed and until clinical resolution of the infection.

*Immunization*

Attenuated vaccines are contraindicated, although therapeutic vaccination windows may be opened if considered necessary and feasible.[23]

*Perioperative considerations*

Treatment with JAK inhibitors may increase the risk of perioperative infection, therefore treatment should be discontinued seven days prior to a scheduled surgical intervention.

No studies have been conducted to determine when it is appropriate to reintroduce treatment after surgery. However, various studies accords in that the decision to restart treatment should be taken on the basis of clinical aspects. Generally, it is recommended to wait until the wound has closed and there are no signs of infection. This period usually lasts for at least two weeks.

In the case of emergency surgery, when treatment can obviously not be discontinued for the established period, antibiotic prophylaxis should be extended to reduce the risk of serious infection.[24]

Table 1 summarises the infection-related factors that should be evaluated before and during treatment with a JAK inhibitor.[23–25]

As noted above, the risk of infection associated with these treatments depends on the mechanism of action. As such, the prior evaluation and follow-up is different for PDE4 inhibitor and JAK inhibitors, as shown in Table 2.

## COVID-19 in patients being treated with targeted synthetic DMARDs

Patients receiving immunosuppressive therapy may be at higher risk of SARS-CoV-2 infection compared with the general population. However, it is also possible that such treatment is associated with a reduction in the complications of serious COVID-19.[27] Indeed, baricitinib is recommended by the World Health Organisation as a therapeutic option for serious COVID-19.[28] In patients with inflammatory bowel disease or rheumatoid arthritis, as in the general population, it has been observed that the risk factors for developing serious COVID-19 are obesity, age, diabetes, cardiovascular disease, obstructive pulmonary disease and chronic kidney disease.[29–31]

However, there are insufficient data to show that apremilast or JAK inhibitors increase the risk of COVID-19 infection and its complications. Further studies are required to better understand this risk.

***The vaccination status must be evaluated, a screening for infection with hepatitis B and tuberculosis performed and active infection ruled out before starting JAK inhibitors***

***Attenuated vaccines are contraindicated in patients receiving immunosuppressive therapy***

Patients treated with JAK inhibitors are considered to be a priority group for vaccination with the booster dose against COVID-1932 and are candidates for the administration of new antiviral alternatives against infection.[33]

## Vaccines and recommendations

Vaccination should be planned from the time of diagnosis and before starting treatment with a JAK inhibitor.[34,35] However, a delay in treatment to vaccinate is not justified if urgent.

Attenuated vaccines are contraindicated in patients receiving immunosuppressive therapy and must be administered at least four weeks prior to the start of treatment, or a certain period must be left once treatment has finished. In the case of tofacitinib, vaccines may be administered two weeks before, although it is preferable to increase this period to four weeks.[11]

Inactivated vaccines are safe and not contraindicated in patients receiving immunosuppressive therapy. These include the trivalent influenza, pneumococcal (PCV13, PSV23), hepatitis A, hepatitis B, Haemophilus influenzae B, human papillomavirus virus, tetanus and herpes zoster vaccines.

**Table 1.** Infection-related factors to be evaluated before and during treatment with a JAK inhibitor.

| | |
|---|---|
| **Before starting treatment** | **Interview**<br>· Prior history of bacterial, fungal or herpes simplex virus infection<br>· Risk of latent or active tuberculosis infection<br>· Hepatitis B immunisation status<br>· Review disease history and vaccination against measles, mumps, rubella and chickenpox<br>· History of travel or future travel to regions with endemic infectious diseases |
| | **Physical examination**<br>· Signs of active local or systemic infection |
| | **Laboratory tests**<br>· Complete blood count and c-reactive protein<br>· Serology: hepatitis A, B and C virus, Epstein-Barr virus, HIV, measles, mumps and rubella<br>· Varicella zoster serology in patients with no prior immunisation history<br>· Urine analysis if prior urinary infections or compatible symptoms |
| | **Tuberculosis screening**<br>· Tuberculin test and/or interferon-γ release assay (IGRA)<br>· If screening test positive, perform chest X-ray. Treat only if screening test positive (isoniazid 5 mg/kg/day up to a maximum of 300 mg/day with vitamin B supplementation for 9 months. In the case of intolerance: rifampicin at a dose of 10 mg/kg/day for 4 months) |
| **During treatment** | **Active bacterial or viral infection**<br>Discontinue treatment until resolved |
| | **Immunization**<br>Attenuated vaccines are contraindicated |
| | **Scheduled surgical intervention**<br>Discontinue seven days prior to the intervention |
| | **Urgent surgical intervention**<br>Extend antibiotic prophylaxis to reduce the risk of serious infection |

**Table 2.** Summary of infection risks associated with targeted synthetic DMARDs[26].

| Drug | TBC | Herpes zóster | HBV | Other viral infections | PJP | COVID-19 | Assessment prior to treatment | Assessment during treatment | Other relevant risks |
|---|---|---|---|---|---|---|---|---|---|
| **PDE4 inhibitor**<br>**Apremilast** | No | No | No | ND | ND | ND | Tuberculosis screening not required. | No specific tests. | Mood alterations.<br>Weight loss.<br>Serious cardiovascular events. |
| **JAK inhibitors**<br>**Abrocitinib**<br>**Baricitinib**<br>**Filgotinib**<br>**Tofacitinib**<br>**Upadacitinib** | YES | YES | YES | CMV<br>PME<br>EBV | YES<br>(in the presence of other risk factors*) | ND | Prior history of infections.<br>Vaccination status. (measles, rubella, mumps, chickenpox).<br>HBV immunisation.<br>Tuberculosis screening.<br>Rule out systemic or local infection. | Suspend if active infection until resolved.<br>Attenuated vaccines are contraindicated.<br>Interrupt treatment 7 days prior to scheduled surgery. | VTE (DVT and PE)<br>Haematological disorders.<br>Serious cardiovascular events.<br>Malignant neoplasm.<br>ILD<br>GI perforation. |

TBC: Tuberculosis
HBV: Hepatitis B virus
PJP: *Pneumocystis jirovecii* pneumonia
PDE4: Phosphodiesterase-4
ND: Not determined
JAK: Janus kinase
CMV: Cytomegalovirus
PME: Progressive multifocal encephalopathy
EBV: Epstein-Barr virus
VTE: Venous thromboembolism
DVT: Deep vein thrombosis
PU: Pulmonary embolism
ILD: Interstitial lung disease
GI: Gastrointestinal

(*) Risk factors: prior or concomitant treatment with corticosteroids, low lymphocyte count, high-dose JAK inhibitor[26].

**Measures to minimise risk of serious side effects with Janus kinase inhibitors.**
The Spanish Agency of Medicines and Medical Devices (AEMPS). November 2, 2022.

EMA has concluded that the increased risk of major adverse cardiovascular events, venous thromboembolism, malignancy, serious infections, and all-cause mortality identified in the ORAL Surveillance study should be considered a class effect for all JAK inhibitors.

These medicines should only be used in the following patients if no suitable treatment alternatives are available: those aged 65 years or above, those who are current or past long-time smokers, those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or those with other malignancy risk factors.

Cautious use is also recommended in patients with known risk factors for venous thromboembolism other than those listed above.

If JAK inhibitors are needed in patients with these risk factors, a lower dose may be recommended.

It is recommended that healthcare professionals carry out periodic examinations of their patients' skin to check for skin cancer.

The vaccines recommended in immunocompromised adults, which is the case for patients with immune-mediated inflammatory diseases who are about to start treatment with a JAK inhibitor, are shown in Table 3[36,37].

**Table 3.** Vaccination recommendations in patients receiving immunosuppressive therapy.

| Infection | Recommended vaccine | Regimen | Booster dose |
|---|---|---|---|
| Pneumococcus *(Streptococcus pneumoniae)* | PCV13 and PSV23 | Regimen sequence: PCV13+PSV23 (recommended interval 12 months, minimum 8 weeks) | PSV23, 5 years since previous dose |
| Influenza *(Virus influenza)* | Inactivated | 1 Annual dose | |
| Hepatitis A | HA | If risk* and hepatotoxicity 2 doses, regimen 0, 6 months | |
| Hepatitis B | HB | If risk** and hepatotoxicity 3 doses, 0, 1 and 6 months | |
| Herpes zoster | RZV | 2 Doses separated by at least 2 months | |
| SARS-CoV-2 | mRNA | Three doses, with the second separated ≥21 days or 28 days*** from the first, and the third separated ≥28 days from the second | One dose at 5 months from the last dose |

PCV13: 13-valent conjugated pneumococcal vaccine.
PSV23: 23-valent pneumococcal polysaccharide vaccine.
HA: hepatitis A.
HB: hepatitis B.
RZV: recombinant zoster vaccine.
(*) Vaccination if high risk of exposure (sexual, parenteral drug users, chronic liver disease, occupational risk).
(**) Vaccination if high risk of exposure (sexual, parenteral drug users, contact with AgHBs carrier, HIV or HCV infection, persons receiving blood derivatives or healthcare personnel with occupational risk).
(***) Depending on the vaccine used: 21 days for Comirnaty®, 28 days for Spikevak®.

### Influenza *(influenza virus)*

The morbidity of flu is higher in immunocompromised patients.[38] Patients with inflammatory bowel disease or rheumatoid arthritis have a higher probability of suffering complications, such as hospitalisation or pneumonia, if they get the flu.[35]

Published data indicate that the immune response to the flu vaccine is not affected by the use of anti-TNF, tocilizumab or tofacitinib.[39–41]

Patients receiving immunosuppressive therapy, such as JAK inhibitors, are one of the groups for which flu vaccination is recommended. The trivalent inactivated vaccine should be used as per the standard immunisation scheme.[36]

### Pneumococcus *(Streptococcus pneumoniae)*

Streptococcus pneumoniae is the main cause of pneumonia and meningitis in western countries. The risk of pneumococcal infection is significantly higher in patients with rheumatoid arthritis or inflammatory bowel disease.[35]

There are currently two vaccine variants available: the polysaccharide pneumococcal (PSV23) and the conjugated pneumococcal (PCV13). In the case of adult patients receiving immunosuppressive therapy and who have not been immunised previously with PSV23 or PCV13, it is recommended to administer both antipneumococcal vaccines available sequentially, starting with the conjugated vaccine, in order to maximise serotype coverage.[42]

### Herpes zoster

Herpes zoster is a disease caused by reactivation of varicella zoster virus, which is latent in the dorsal root lymph nodes. Its incidence increases markedly with the presence of immunosuppression. Although it presents low mortality, its complications, such as postherpetic neuralgia, may cause disability and reduce the quality of life of people with it.[43,44]

There are currently two vaccines authorised in Spain for the prevention of herpes zoster and postherpetic neuralgia:

- **The attenuated live vaccine (ZVL),** authorised by the EC in 2006,[45] indicated in people aged more than 50 years. It is administered as a single dose and is contraindicated in primary or acquired immunodeficiency states.

- **The adjuvant recombinant vaccine (RZV),** authorised by the EC in 2018, indicated in people older than 50 years of age and older than 18 years with a risk factor for immunodeficiency. It is administered in two doses.

**Antiviral prophylaxis is indicated in patients with chronic HBV infection**

The RZV vaccine has been shown to significantly reduce the incidence of herpes zoster and postherpetic neuralgia in immunocompromised patients. Several studies have shown that the efficacy of this vaccine is not affected by underlying diseases such as chronic obstructive pulmonary disease, diabetes, depression or chronic kidney disease. The safety profile in people with risk factors for immunosuppression is similar to that in general population.[46]

The above explains why adult patients receiving treatment with JAK inhibitors are one of the priority groups for vaccination against herpes zoster with RZV vaccine, as per the latest recommendations approved by the Public Health Commission in March 2021.[47]

In April 2022, the Department of Health of the Government of Navarre began to administer the RZV vaccine to collectives with risk factors, such as adult patients receiving treatment with JAK inhibitors.

The administration regimen in these patients consists of two intramuscular doses with a minimum interval of two months between them, if possible, prior to starting treatment. It can be administered concomitantly with the seasonal flu vaccine, pneumococcal vaccine (PCV13 and PSV23), low-load dTpa (diphtheria, tetanus, whooping cough) vaccine or COVID-19 vaccines at different injection sites. There are no concomitant administration data for vaccines other than those mentioned above, therefore a minimum interval of seven days is recommended prior to the administration of additional vaccines.

### Hepatitis B

Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV). This infection may become chronic and leads to an increased risk of liver failure, hepatocarcinoma or cirrhosis.

Different studies have shown that the risk of HBV reactivation in patients with inflammatory bowel disease and

rheumatoid arthritis is increased after treatment with immunosuppressants.[48]

The risk and reactivation kinetics differ depending on the immunosuppressive therapy used and the infection status, therefore the individual risk must be stratified to be able to implement appropriate preventive measures.[49]

A screening of the infection status should be performed using serological markers (surface antigen [HBsAg], anti-core antibody [HBcAc] and anti-surface antigen antibody [HBsAc]) before starting immunosuppressive therapy and seronegative patients with no signs of infection should be vaccinated.[25,49]

Moreover, the viral load should be determined in HBsAg-positive patients. In the case of patients with signs of chronic infection (HBsAg+, HBcAc+ and HBsAc -), prophylaxis with entecavir 0.5 mg/day or tenofovir 245 mg/day is indicated, and this should be introduced at least two weeks prior to starting treatment with the JAK inhibitor and continued for 12 months after its withdrawal. In the case of patients with signs of past infection (HBsAg-, HBcAc+, with or without HBsAc), HBV reactivation occurs very rarely, therefore routine antiviral prophylaxis is not recommended.[25,4]. In any case, transaminase and HBV-DNA should be monitored to detect a possible reactivation of HBV infection.[25]

Vaccination against HBV is recommended in seronegative patients with no signs of infection. The administration regimen consists of three doses of the recombinant vaccine at 0, 1 and 6 months. The response to the vaccine should be measured at one month from completing the vaccination regimen. It is possible that the efficacy of the HBV vaccine is reduced in these patients due to the autoimmune disease itself and immunosuppresive treatment (prior or current). In such cases, vaccine regimens with four doses or a higher antigen load (double dose of the normal regimen) may be considered.[25]

## Tuberculosis

Tuberculosis is an infection caused by *Mycobacterium tuberculosis* which, after the initial infection, may persist in an inactive latent state. Although the infection is asymptomatic in this state, there is nevertheless a risk of reactivation depending on the patient's immunological state.[50]

In Spain, more than 10% of patients candidates to receive immunosuppressive therapy present latent tuberculosis.[51,52] In a grouped analysis of clinical trials and registration studies, a tuberculosis infection rate of 0.2 per 100 persons/year was observed for tofacitinib and 0.15 for baricitinib.

The recommendations to screen for latent tuberculosis and treat it before administering immunosuppressive therapy have reduced the risk of active tuberculosis by 78–90%.[52] Two techniques are recommended in Spain for diagnosis: the interferon gamma release assay (IGRA) and the tuberculin test.[50] In addition, the history of tuberculosis must also be evaluated.[25,53] A chest X-ray should only be performed in the case of a positive screening test.

A study performed in Spain in 2018 highlighted the low degree of adherence to these recommendations (56%), with only 36% of respondents requesting the recommended diagnostic tests. A more exhaustive adherence to these recommendations is expected to help to reduce the incidence of tuberculosis in patients candidates to receive biological treatments and JAK inhibitors.[52]

In the case of latent tuberculosis, it is recommended to delay immunosuppressive therapy for at least three weeks after starting the anti-tuberculosis treatment, except in the event of a medical emergency and upon advice from the specialist.[25]

The most appropriate treatment for active tuberculosis is defined as at least six months of treatment with first-line drugs, including at least two months with the combination rifampicin + isoniazid + pyrazinamide + ethambutol.[50]

In the case of latent tuberculosis, the recommended regimen is isoniazid at a dose of 5 mg/kg/day up to a maximum of 300 mg/day with vitamin B supplements for at least nine months. In the event of intolerance, rifampicin at a dose of 10 mg/kg/day for four months is recommended.[54] It should be noted that rifampicin is a CYP3A4 inducer and may reduce the exposure to JAK inhibitors, thereby decreasing their effectiveness.[55]

## Situation in the Community of Navarre

It can be seen from Figure 1 that the number of patients in treatment with apremilast and JAK inhibitors has increased over the past few years as these drugs have begun to be marketed in Spain. Tofacitinib remains the most widely used JAK inhibitor as we have the most experience with it. During the past year, the number of patients treated in the Navarre Health Service with JAK inhibitors for rheumatic disease was higher than those treated with apremilast, as can be seen in Figure 2. This may be due to the fact that apremilast has a more limited efficacy than JAK inhibitors in rheumatic diseases. The use of JAK inhibitors in dermatology was low compared to the use of apremilast as the latter is indicated for both psoriasis and psoriatic arthritis. In addition, the use of JAK inhibitors in atopic dermatitis is recent.

The Spanish pharmacovigilance adverse reactions database (FEDRA) was consulted to obtain the suspected adverse drug reaction (ADR) reports with the criterion of serious infections or infestations related to apremilast or JAK inhibitors. From July 2014 to June 2022, 18 ADRs with apremilast that complied with these criteria were reported, compared with 39 for tofacitinib, 31 for baricitinib and six for upadacitinib.

**Figure 1.** Number of patients in treatment with apremilast and JAK inhibitors since they were marketed in Spain. Hospital Pharmacy database of the Navarre Health Service.

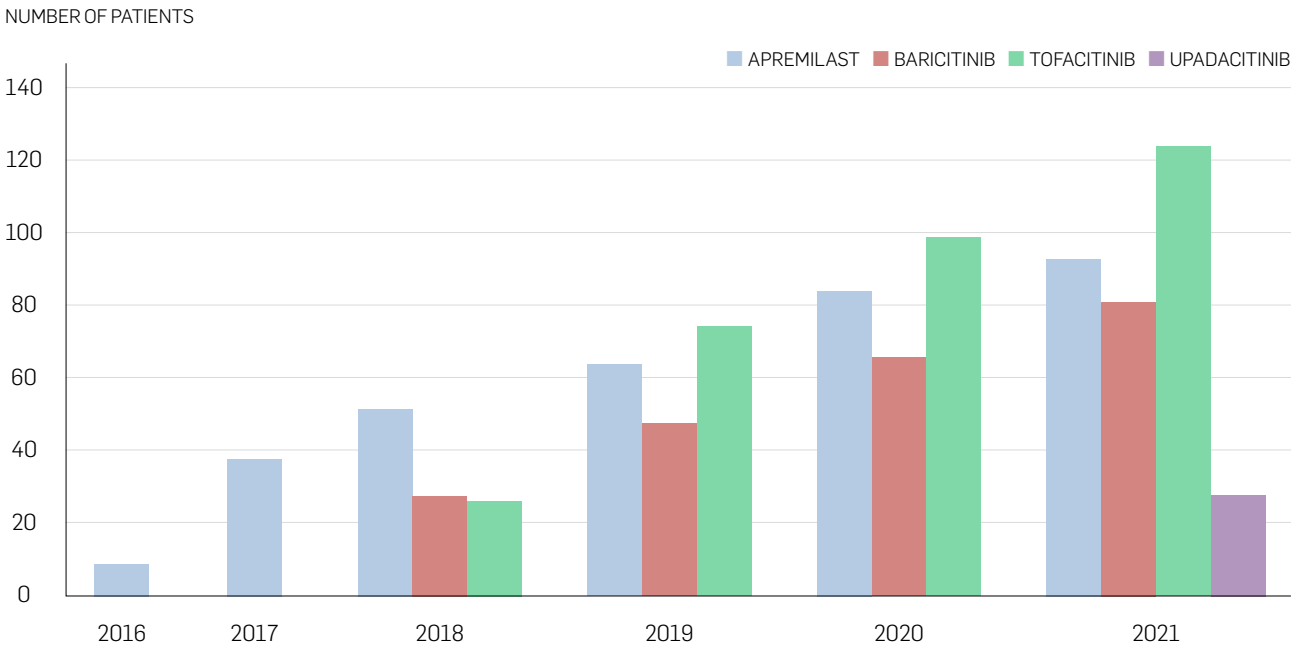
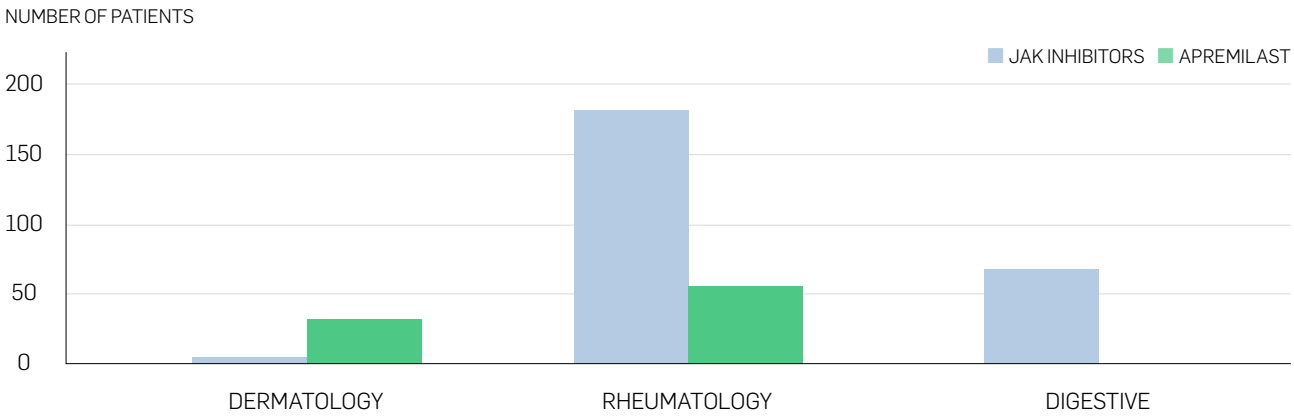


**Figure 2.** Number of patients treated with apremilast or JAK inhibitors by the Navarre Health Service in the last year (June 2021–June 2022) by medical service.




## Conclusions

**Patients with immune-mediated inflammatory diseases present a higher risk of developing infections compared with the general population.**

**Treatment with immunosuppressive drugs increases the risk of serious and opportunistic infections.**

**There is no evidence for an increased risk of serious infections, including opportunistic infections, associated with the use of apremilast.**

**Treatment with JAK inhibitors has been associated with an increase in infection risk, including reactivation of tuberculosis, herpes zoster and hepatitis B, amongst other infections.**

**There is currently insufficient data to demonstrate that apremilast or JAK inhibitors increase the risk of COVID-19 infection and its complications.**

**The patient's vaccination status should be evaluated at diagnosis, administering the vaccines required, screening for hepatitis B infection and latent tuberculosis should be performed, and an active systemic or local infection should be ruled out prior to starting immunosuppressive therapy.**

**The inactivated vaccines recommended for patients treated with JAK inhibitors are pneumococcus, influenza, hepatitis A, hepatitis B, herpes zoster and SARS-CoV-2. Attenuated live vaccines are contraindicated in these patients. On occasions, it is possible to discontinue immunosuppressive therapy temporarily to create a therapeutic window for vaccine administration.**

**It is important that both healthcare professionals and patients are aware of the infection-prevention measures and recognise the signs and symptoms of infection before and during treatment with these drugs.**

## References


1. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum*. 2002;46(9):2287-2293. https://doi.org/10.1002/art.10524

2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum*. 2002;46(9):2294-2300. https://doi.org/10.1002/art.10529

3. Grupo de trabajo de la GUIPAR. *Guía de Práctica Clínica Para El Manejo de Pacientes Con Artritis Reumatoide*. 2019th ed. (Sociedad Española de Reumatología, ed.).; 2019. https://www.ser.es/wp-content/uploads/2019/03/Guia-de-Practica-Clinica-para-el-Manejo-de-Pacientes-con-Artritis-Reumatoide.pdf

4. Fernández-Ruiz M, Meije Y, Manuel O, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction). *Clin Microbiol Infect*. 2018;24 Suppl 2:S2-S9. https://doi.org/10.1016/j.cmi.2018.01.029

5. Irigoyen I, Goñi O. Riesgos infecciosos asociados a los fármacos biológicos utilizados en enfermedades inflamatorias de origen inmune. *Bol Inf Farm Navar*. 2020;28(3):1-17. http://www.navarra.es/home_es/Temas/Portal+de+la+Salud/Profesionales/Documentacion+y+publicaciones/Publicaciones+tematicas/Medicamento/BIT/Vol+28/BIT+28+N+3.htm

6. Schafer PH, Parton A, Capone L, et al. Apremilast is a selective PDE4 inhibitor with regulatory effects on innate immunity. *Cell Signal*. 2014;26(9):2016-2029. https://doi.org/10.1016/j.cellsig.2014.05.014

7. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Apremilast (Otezla®)*.; 2015. https://cima.aemps.es/cima/dochtml/ft/114981001/FT_114981001.html

8. Agencia Europea del Medicamento (EMA). *Summary of Risk Management Plan for Apremilast*.; 2022. https://www.ema.europa.eu/documents/rmp-summary/otezla-epar-risk-management-plan-summary_en.pdf

9. Agencia Española de Medicamentos y Productos Sanitarios. *Informe de Posicionamiento Terapéutico de Apremilast (Otezla®) En Psoriasis Cutánea y Artritis Psoriásica*.; 2015. https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-apremilast-Otezla.pdf?x81697

10. Hagberg KW, Persson R, Vasilakis-Scaramozza C, et al. Herpes Zoster, Hepatitis C, and Tuberculosis Risk with Apremilast Compared to Biologics, DMARDs and Corticosteroids to Treat Psoriasis and Psoriatic Arthritis. *Clin Epidemiol*. 2020;12:153-161. https://doi.org/10.2147/CLEP.S239511

11. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Tofacitinib (Xeljanz®)*.; 2017. https://cima.aemps.es/cima/dochtml/ft/1171178007/FT_1171178007.html

12. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Baricitinib (Olumiant®)*.; 2017. https://cima.aemps.es/cima/pdfs/ft/1161170002/FT_1161170002.pdf

13. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Upadacitinib (Rinvoq®)*.; 2019. https://cima.aemps.es/cima/dochtml/ft/1191404001/FT_1191404001.html

14. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Filgotinib (Jyseleca®)*.; 2020. https://cima.aemps.es/cima/dochtml/ft/1201480001/FT_1201480001.html

15. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD open*. 2020;6(3). https://doi.org/10.1136/rmdopen-2020-001395

16. Agencia Europea del Medicamento (EMA). *Summary of the Risk Management Plan for Tofacitinib*.; 2022. https://www.ema.europa.eu/documents/rmp-summary/xeljanz-epar-risk-management-plan-summary_en.pdf

17. Agencia Europea del Medicamento (EMA). *Summary of Risk Management Plan for Baricitinib*.; 2022. https://www.ema.europa.eu/documents/rmp-summary/olumiant-epar-risk-management-plan-summary_en.pdf

18. Agencia Europea del Medicamento (EMA). *Summary of Risk Management Plan for Upadacitinib*.; 2022. https://www.ema.europa.eu/documents/rmp-summary/rinvoq-epar-risk-management-plan-summary_en.pdf

19. Agencia Europea del Medicamento (EMA). *Summary of Risk Management Plan for Filgotinib*.; 2021. https://www.ema.europa.eu/documents/rmp-summary/jyseleca-epar-risk-management-plan-summary_en.pdf

20. Agencia Europea del Medicamento (EMA). *Informe de Evaluación EPAR de Filgotinib*.; 2021. https://www.ema.europa.eu/documents/variation-report/jyseleca-h-c-005113-ii-0001-epar-assessment-report-variation_en.pdf

21. Aegencia Europea del Medicamento (EMA). *Ficha Técnica Abrocitinib (Cibinqo®)*.; 2021. https://cima.aemps.es/cima/dochtml/ft/1211593009/FT_1211593009.html

22. Simpson EL, Silverberg JI, Nosbaum A, et al. Integrated Safety Analysis of Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis From the Phase II and Phase III Clinical Trial Program. *Am J Clin Dermatol*. 2021;22(5):693-707. https://doi.org/10.1007/s40257-021-00618-3

23. Morel J, Czitrom SG, Mallick A, Sellam J, Sibilia J. Vaccinations in adults with chronic inflammatory joint disease: Immunization schedule and recommendations for patients taking synthetic or biological disease-modifying antirheumatic drugs. *Jt Bone Spine*. 2016;83(2):135-141. https://doi.org/10.1016/j.jbspin.2015.08.008

24. Larrosa García M, Juárez Giménez JC, Lalueza Broto P, Trallero Araguas E. Actualización de las recomendaciones sobre el manejo del tratamiento antirreumático en el perioperatorio de la cirugía de artroplastia de cadera y rodilla. *El Farm Hosp*. 2018;2013:4-12.

25. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2014;8(6):443-468. https://doi.org/10.1016/j.crohns.2013.12.013

26. Reinwald M, Silva JT, Mueller NJ, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). *Clin Microbiol Infect*. 2018;24:S53-S70. https://doi.org/10.1016/j.cmi.2018.02.009

27. Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut*. 2021;70(4):725-732. https://doi.org/10.1136/gutjnl-2020-322539

28. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *BMJ*. 2020;370:m3379. https://doi.org/10.1136/bmj.m3379

29. Marín-Jiménez I, Zabana Y, Rodríguez-Lago I, Marín L, Barreiro-de Acosta M, Esteve M. COVID-19 y enfermedad inflamatoria intestinal: preguntas surgidas de la atención y seguimiento de los pacientes durante la fase inicial de la pandemia (febrero-abril 2020). *Gastroenterol Hepatol*. 2020;43(7):408-413. https://doi.org/https://doi.org/10.1016/j.gastrohep.2020.05.003

30. Neurath MF. COVID-19 and immunomodulation in IBD. *Gut*. 2020;69(7):1335-1342. https://doi.org/10.1136/gutjnl-2020-321269

31. Quartuccio L, Valent F, Pasut E, Tascini C, De Vita S. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: A population-based study in the first two months of COVID-19 outbreak in Italy. *Jt Bone Spine*. 2020;87(5):439-443. https://doi.org/10.1016/j.jbspin.2020.05.003

32. Grupo de Trabajo Técnico de Vacunación del Sistema Nacional de Salud. *Estrategia de Vacunación COVID-19. Actualización 9*.; 2021. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Actualizaciones_Estrategia_Vacunacion/docs/COVID-19_Actualizacion9_Modificada_EstrategiaVacunacion.pdf

33. Agencia Española de Medicamentos y Productos Sanitarios. *Criterios Para Valorar La Administración de Las Nuevas Alternativas Terapéuticas Antivirales Frente a La Infección Por SARS-CoV-2*.; 2022. https://www.aemps.gob.es/medicamentos-de-uso-humano/acceso-a-medicamentos-en-situaciones-especiales/criterios-para-valorar-la-administracion-de-las-nuevas-alternativas-terapeuticas-antivirales-frente-a-la-infeccion-por-sars-cov-2/

34. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(1):39-52. https://doi.org/10.1136/annrheumdis-2019-215882

35. Meroni PL, Zavaglia D, Girmenia C. Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs. *Clin Exp Rheumatol*. 2018;36(2):317-328.

36. Ministerio de Sanidad. Vacunas y Programa de Vacunación. Accessed June 30, 2022. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/programasDeVacunacion/riesgo/home.htm

37. Ministerio de Sanidad. *Guía Sobre Utilización de Vacunas Para Personal Sanitario. Estrategia de Vacunación Frente a COVID-19*.; 2022. https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/docs/COVID-19_Guia_utilizacion_vacunas_personalsanitario.pdf

38. Marín AC, Gisbert JP, Chaparro M. Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease. *World J Gastroenterol*. 2015;21(40):11273-11281. https://doi.org/10.3748/wjg.v21.i40.11273

39. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2014;66(7):1016-1026. https://doi.org/10.1002/acr.22246

40. Friedman MA, Winthrop KL. Vaccines and Disease-Modifying Antirheumatic Drugs: Practical Implications for the Rheumatologist. *Rheum Dis Clin North Am*. 2017;43(1):1-13. https://doi.org/10.1016/j.rdc.2016.09.003

41. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75(4):687-695. https://doi.org/10.1136/annrheumdis-2014-207191

42. Rubin LG, Levin MJ, Ljungman P, et al. Executive Summary: 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. *Clin Infect Dis*. 2014;58(3):309-318. https://doi.org/10.1093/cid/cit816

43. Centro Nacional de Epidemiología. *Situación de La Varicela y Herpes Zóster En España*.; 2014. http://www.isciii.es/ISCIII/es/contenidos/fd-servicios-cientifico-tecnicos/fd-vigilancias-alertas/fd-enfermedades/fd-enfermedades-prevenibles-vacunacion/Informe_situacion_Varicela_HZ__Espana_1998-2012.pdf

44. Johnson RW, Alvarez-Pasquin M-J, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Ther Adv vaccines*. 2015;3(4):109-120. https://doi.org/10.1177/2051013615599151

45. Agencia Europea del Medicamento (EMA). *Ficha Técnica Zostavax*.; 2020. https://www.ema.europa.eu/en/documents/product-information/kyntheum-epar-product-information_es.pdf

46. Agencia Española de Medicamentos y Productos Sanitarios. *Ficha Técnica Shingrix®*.; 2018. https://cima.aemps.es/cima/dochtml/ft/1181272001/FT_1181272001.html

47. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. *Recomendaciones de Vacunacion Frente a Herpes Zoster*.; 2021. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiS7bDUht36AhUCixoKHamGBCAQFnoECAsQAQ&url=https%3A%2F%2Fwww.sanidad.gob.es%2Fprofesionales%2FsaludPublica%2FprevPromocion%2Fvacunaciones%2FprogramasDeVacunacion%2Fdocs%2FHerpesZoster_RecomendacionesVacunacion.pdf&usg=AOvVaw3lUff4H72xMhJh7ILDsRHA

48. Loras C, Gisbert JP, Mínguez M, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut*. 2010;59(10):1340-1346. https://doi.org/10.1136/gut.2010.208413

49. Chen Y-M, Yang S-S, Chen D-Y. Risk-stratified management strategies for HBV reactivation in RA patients receiving biological and targeted therapy: A narrative review. *J Microbiol Immunol Infect*. 2019;52(1):1-8. https://doi.org/10.1016/j.jmii.2017.10.002

50. Mir Viladrich I, Daudén Tello E, Solano-López G, et al. Consensus Document on Prevention and Treatment of Tuberculosis in Patients for Biological Treatment. *Arch Bronconeumol*. 2016;52(1):36-45. https://doi.org/10.1016/j.arbres.2015.04.016

51. Zabana Y, Domènech E, San Román AL, et al. Tuberculous chemoprophylaxis requirements and safety in inflammatory bowel disease patients prior to anti-TNF therapy. *Inflamm Bowel Dis*. 2008;14(10):1387-1391. https://doi.org/10.1002/ibd.20496

52. Quirós S, de la Rosa D, Uranga A, et al. Screening for Latent Tuberculosis Infection in Patients who are Candidate for Biological Therapies in Spain? A Multidisciplinary Survey. *Arch Bronconeumol*. 2018;54(10):510-517. https://doi.org/10.1016/j.arbres.2018.04.004

53. Riestra S, Taxonera C, Zabana Y, et al. Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on screening and treatment of tuberculosis infection in patients with inflammatory bowel disease. *Gastroenterol Hepatol*. 2021;44(1):51-66. https://doi.org/10.1016/j.gastrohep.2020.04.006

54. Rúa-Figuerola, Íñigo; Calvo Alén J, Cuadrado Lozano MJ, Freire González MM, Martínez-Taboada VM., Muñoz Fernández S, Úcar Angulo E. *Manual SER de Diagnóstico y Tratamiento de Las Enfermedades Reumáticas Autoinmunes Sistémicas*. Vol 1.; 2014. https://www.ser.es/wp-content/uploads/2015/09/Manual_ERAS.pdf

55. Zhang Z, Deng W, Wu Q, Sun L. Tuberculosis, hepatitis B and herpes zoster in tofacitinib-treated patients with rheumatoid arthritis. *Immunotherapy*. 2019;11(4):321-333. https://doi.org/10.2217/imt-2018-0113

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