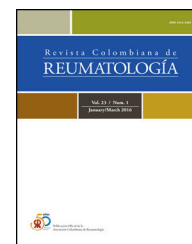




Asociación
Colombiana de
Reumatología®

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma



Consensus statement

Consensus for risk management in the prescription of biologic therapies or targeted synthetic antirheumatic drugs: Colombian Association of Rheumatology 2023

Consenso para la gestión de riesgo en la prescripción de terapias biológicas o de antirreumáticos sintéticos con blanco dirigido: Asociación Colombiana de Reumatología 2023

Elías Gonzalo Forero Illera^{a,b,*}, Andrés Ricardo Fernández Aldana^{b,c},
Daniel Gerardo Fernández Ávila^{b,d}, Edwin Antonio Jáuregui Cuartas^{b,e},
Gloria Vásquez^{b,f}, Monique Chalem^{b,g,h}, Wilson Bautista Molano^{b,g,h,i}

^a Facultad Medicina, Universidad del Norte, Barranquilla, Colombia

^b Asociación Colombiana de Reumatología (Asoreuma), Bogotá, Colombia

^c Unidad de Reumatología y Medicina Interna, Inmumar IPS, Ibagué, Colombia

^d Unidad de Reumatología, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia

^e Unidad de Reumatología, Riesgo de Fractura S.A Cayre IPS, Bogotá, Colombia

^f Sección de Reumatología de la Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

^g Departamento de Reumatología, Hospital Universitario Fundación Santa Fe, Bogotá, Colombia

^h Departamento de Reumatología, Universidad El Bosque, Bogotá, Colombia

ⁱ Facultad de Medicina, Universidad Militar Nueva Granada, Bogotá, Colombia

Introduction

Modifying the immune response induced by biological therapies and the recently approved JAK inhibitors has significantly altered the treatment and monitoring of chronic autoimmune and inflammatory diseases.^{1,2} While these agents are generally well-tolerated, post-marketing surveillance data reveal a frequent association with adverse events, including allergic, immunological, infectious, and other unwanted reactions.³

Therefore, effective risk management in therapy involves closely monitoring patients to identify, prevent, and minimize events that could potentially compromise their safety during the use of these drugs.⁴

In 2016, the Asociación Colombiana de Reumatología (ASOREUMA) published a set of recommendations for the safe use of biological therapies in clinical practice.⁵ In Colombia, the estimated prevalence of patients with rheumatoid arthritis receiving biological therapies is 14.7%, while 1.3% are prescribed JAK inhibitors.⁶

DOI of original article: <https://doi.org/10.1016/j.rcreue.2024.01.007>.

* Corresponding author.

E-mail address: eforero64@gmail.com (E.G. Forero Illera).

2444-4405/© 2024 Published by Elsevier España, S.L.U. on behalf of Asociación Colombiana de Reumatología.

The purpose of this document is to provide updated information to help rheumatologists, related specialists, and other healthcare professionals effectively manage the risks associated with the use of biological therapies and targeted synthetic antirheumatic drugs in patients with chronic inflammatory and autoimmune diseases. A panel of experts from ASOREUMA, after reviewing the available evidence, presents recommendations for managing risks when prescribing these therapies in various clinical scenarios, such as cancer, surgery, tuberculosis (TB), hepatitis, vaccination, cardiovascular disease, pregnancy, and breastfeeding. Implementing these recommendations in daily clinical practice aims to minimize potential adverse effects associated with these treatments and ensure proper follow-up care for patients.

Methods

Participants and consensus formulation

A multidisciplinary development group, consisting of eight clinical experts from rheumatology, infectious diseases, and pulmonology, was formed. All members had extensive experience in prescribing and monitoring therapy with biologic or targeted synthetic antirheumatic drugs in patients with various diseases. An independent methodological team (Epithink Health Consulting) supported the development of the consensus. All members of the development group disclosed their interests, and none had conflicts of interest regarding their participation in the consensus (see Appendix A, Supplementary material 1).

During a group session, the team defined the questions to be updated and the new questions to be addressed as part of this consensus. The selection criteria were based on the following factors: 1) relevance to current clinical practice, 2) new relevant evidence on effectiveness and safety, 3) new relevant evidence on changes in the clinical context, 4) the need to update a specific question, and 5) the priority for updating that question.

Searching and selecting evidence

Systematic searches for relevant evidence were conducted for each research question. The evidence that informs this consensus is presented in the Supplementary Material. Different search strategies were employed for each topic, aiming to achieve the best balance between sensitivity and specificity. These strategies were written in English. Literature searches were performed in the MEDLINE-PubMed database (including the In-Process & Other Non-Indexed Citations section); EMBASE (from 1947 to the search date); EBM Reviews-Cochrane Database of Systematic Reviews (since 2005); the Database of Abstracts of Reviews of Effects; and LILACS.

Two methodological experts screened the search results by title and abstract, applying predefined selection criteria based on the guiding thematic questions (Appendix A, Supplementary material 2). Posters, abstracts, and letters to the editor were excluded from the review. Any disagreements between reviewers were resolved by consensus. The selected references were then reviewed in full text, and their inclusion was deter-

mined in collaboration with the clinical experts. The results of this process are summarized in a PRISMA⁷ flowchart for each reviewed topic (Appendix A, Supplementary material 2).

Delphi method

The evidence for each question was reviewed, and relevant information was extracted to develop a questionnaire. In the next phase, eight additional clinical experts from different disciplines joined the panel. The first round of consensus was conducted in a blinded, virtual, and asynchronous manner. Based on the evidence and clinical experience, the experts assessed their level of agreement with risk management statements related to the prescription of biological therapies or targeted synthetic antirheumatic drugs in Colombia, using a Likert scale. The group's level of agreement was determined through analysis of the first round (Appendix A, Supplementary material 3). Following this, a synchronous session was held to discuss the contents and conduct a second round of assessments, leading to the formulation of the final recommendations.

Other topics that were not subject to updates can be found in the consensus document *Risk Management for the Prescription of Biological Therapies*.⁵

Ethical considerations

This study did not require approval from an ethics committee or informed consent, as it did not involve research subjects.

Results

Recommendations for risk management in the use of biological therapies or targeted synthetic antirheumatic drugs

Latent tuberculosis (LTB)

Current guidelines recommend screening for latent tuberculosis (LTB) in all individuals being considered for treatment with targeted biologic or synthetic agents, regardless of their TB risk factors.⁸ The World Health Organization (WHO) recommends using both the purified protein derivative (PPD) skin test and the interferon-gamma release assay (IGRA) to diagnose LTB and reduce the risk of false negatives.⁹ Evidence, largely from observational studies, suggests that adding IGRA to standard practice^{10,11} may improve the identification of LTB cases.¹²⁻¹⁴ However, in Colombia, where IGRA availability is limited, screening and follow-up continue to rely on PPD testing and chest X-rays.¹⁵ This is especially important since a negative IGRA or PPD result does not fully exclude active TB or rule out LTB. In all cases, clinical professionals are encouraged to assess each patient's TB risk and the type of therapy being considered about the likelihood of TB reactivation, considering the high frequency of positive tuberculin tests in Colombian patients with rheumatoid arthritis, even before starting biological therapy.¹⁶

Screening should be periodically reassessed during therapy with biologics or synthetic targeted antirheumatic drugs, especially if risk factors emerge or change over time. While

Table 1 – Summary of recommendations on latent tuberculosis and the use of biological therapies or targeted synthetic antirheumatic drugs.

Recommendation	Level of agreement
Before starting therapy with biologics or targeted synthetic antirheumatic drugs	
1 Conduct a thorough medical history to assess potential exposure to tuberculosis (TB), signs and symptoms of the disease, and the use of glucocorticoids.	93%
2 Screen for latent tuberculosis in all patients.	100%
3 Inform patients about the risk of TB reactivation or the development of new TB during treatment with these therapies.	100%
Tests for Screening	
4 The preferred method for latent TB detection is an interferon-gamma release assay (IGRA) combined with chest X-rays.	54%
5 If IGRA is unavailable, perform a tuberculin skin test (PPD). If the result is negative, a repeat test is recommended to check for a possible booster effect.	72%
6 If the IGRA result is indeterminate, the test should be repeated one to three weeks after the initial test.	93%
7 Latent tuberculosis screening should be repeated annually while the patient is receiving biologic or targeted synthetic antirheumatic therapy.	90%
Treatment in Patients Diagnosed with Latent TB	
8 In subjects starting treatment for latent TB, monthly liver function tests should be performed, or more frequently if hepatitis symptoms arise.	100%
9 Multidisciplinary care should involve, when necessary, an infectious disease specialist, pulmonologist, or TB expert.	73%
10 The treatment regimen for latent TB in individuals initiating biologic or synthetic targeted therapy should adhere to national guidelines.	100%
11 Decisions regarding the reinitiation of biological agents or JAK inhibitors should be individualized, considering the risk of TB reactivation, hepatotoxicity, the severity of the underlying condition, and the patient's preferences.	93%
12 For patients at very high risk of TB, preference should be given to non-anti-TNF agents (e.g., rituximab, tocilizumab, or abatacept) over anti-TNF agents.	93%

there is no consensus on the exact frequency of reassessments, annual monitoring is generally recommended,^{17–22} particularly in countries with a high prevalence of TB,⁸ even for those receiving isoniazid prophylaxis.^{23–25}

Various regimens are available for treating LTB, including isoniazid^{9,26–28} alone or in combination with rifampicin²⁸ or rifapentine.⁸ This consensus panel supports adherence to national guidelines, which recommend six months of self-administered isoniazid treatment with monthly follow-ups, or a short-term, weekly regimen with isoniazid and rifapentine for three months under supervised treatment.¹⁵ Although chemoprophylaxis studies suggest that TB reactivation cannot always be fully prevented during long-term anti-tumor necrosis factor (TNF) therapy, periodic assessments are necessary to detect reactivation cases during biological therapy.²⁹

There is evidence of an increased risk of TB reactivation with products such as monoclonal antibodies against TNF,^{30–35} followed by JAK inhibitors and agents targeting interleukin (IL-1).³⁶ Studies of biological agents other than anti-TNF therapies have limitations in quality and performance, particularly

in low TB-prevalence settings, leading to an assumption of a theoretical, but lower, risk of TB reactivation.^{37–40} The risk of reactivation or *de novo* TB appears to be relatively low with treatments such as apremilast, ustekinumab, secukinumab, and rituximab. Nonetheless, LTB screening should always precede the initiation of biological therapy or targeted synthetic antirheumatic drugs,⁴¹ particularly as the use of immunosuppressive drugs like glucocorticoids may increase the risk of TB.

The evidence concerning the optimal timing for starting or restarting biological therapies in patients undergoing LTB treatment is not well-defined and remains variable.^{23,42} Most studies suggest that biologics can be initiated or resumed three to six weeks after starting LTB chemoprophylaxis.^{28,43} However, this timing should be individualized based on factors such as the patient's risk of developing active TB, the potential for hepatotoxicity with LTB treatment, the severity of the underlying disease, and patient preference.⁴⁴ Table 1 summarizes the recommendations for monitoring and treating LTB.

Table 2 – Summary of recommendations in the context of cancer and the use of biological therapies or targeted synthetic antirheumatic drugs.

Recommendation	Level of agreement
13 In patients with active cancer, the opinion of 100% an oncologist should be sought before initiating any biological DMARD or targeted synthetic antirheumatic drugs.	
14 In subjects with a history of cancer who require biological or synthetic targeted therapy, it is recommended to prioritize the use of rituximab, abatacept, and tocilizumab over anti-TNF and synthetic targeted antirheumatic drugs.	100%
15 Individuals with a history of cancer who are receiving biological therapies or targeted synthetic antirheumatic drugs should be monitored for signs of non-melanoma skin cancer or other types of neoplasms.	100%

Cancer

Evidence from meta-analyses of clinical trials⁴⁵⁻⁴⁸ generally supports the safety of biologic therapies (anti-TNF,⁴⁹⁻⁵² JAK inhibitors, IL-17A inhibitors,⁵³ IL-23A inhibitors,⁵³ IL-6 inhibitors,^{49,51,54} rituximab,^{49,50,55} IL-1 inhibitors,⁵⁰ and abatacept⁵⁶) in patients with a history of malignancy. However, some cohort registries suggest, though inconclusively, an increased risk of malignancy with long-term use of anti-TNF therapy.^{49,55} These studies recommend against the use of biologic drugs in patients with active cancer,⁴⁹ while some guidelines advise against using anti-TNF therapies in patients with pre-existing cancer, preferring instead conventional synthetic disease-modifying antirheumatic drugs (DMARDs), rituximab, abatacept, or tocilizumab.⁴⁹

When considering the use of biologic or targeted synthetic antirheumatic drugs in subjects with a history of cancer, several factors must be taken into account. These include an individualized assessment of patient values and preferences, the stage of the disease, prognosis, potential for cure, life expectancy, and quality of life.⁴⁹ It is also crucial to assess potential interactions between chemotherapy, glucocorticoids, the type of cancer, and the use of biologic or targeted synthetic antirheumatic drugs, as well as the overall risk-benefit profile of starting these therapies. Similarly, the panel considered that, in cases of active cancer and high disease activity, the involvement of an oncologist in the therapeutic decision-making process is essential. Table 2 outlines the recommendations for risk management in patients with cancer.

Viral hepatitis

Based on the evidence, due to the potential risk of hepatitis B virus (HBV) reactivation associated with therapy, all patients should be tested for viral hepatitis before initiating biologic or synthetic targeted agents.⁵⁷ Testing for HBV surface antigen (HBsAg), anti-HBV surface antigen antibody (HBsAb),

Table 3 – Summary of recommendations regarding viral hepatitis and the use of biological therapies or targeted synthetic antirheumatic drugs.

Recommendation	Level of agreement
Before starting therapy with biological or synthetic targeted drugs	
16 Perform tests to detect HBV and HCV, including hepatitis B surface antigen, anti-hepatitis B surface antigen antibodies, and anti-core and anti-hepatitis C antibodies.	100%
17 Measure antibodies against hepatitis B surface antigen to determine vaccination status.	100%
18 For patients with a positive result on any screening test, request a viral load test and refer them to a hepatologist or infectious disease specialist.	100%
19 For individuals with a history of hepatitis B or C, an interdisciplinary assessment should be conducted with an infectious disease specialist or hepatologist to determine the best therapeutic option.	93%

or anti-HBV core antibody (HBcAb) is recommended.⁵⁸ In patients with positive test results, HBV-DNA levels should be assessed to differentiate between active carriers, who should be treated before starting biologic or synthetic targeted antirheumatic drugs. For inactive HBV carriers, prophylactic treatment should be initiated before starting immunosuppressive therapy⁵⁹ and continued for at least six to twelve months after completing treatment with immunosuppressive drugs.^{57,60}

While studies indicate a very low risk of hepatitis C virus (HCV) reactivation, particularly with anti-TNF agents, testing for anti-HCV antibodies and, if positive, HCV-RNA levels should be conducted in all patients receiving biologic or synthetic targeted therapies.^{17,61} Patients with detectable HCV-RNA should be monitored during treatment and referred to a hepatologist or infectious disease specialist for antiviral therapy as needed.^{62,63} Table 3 provides a summary of recommendations related to viral hepatitis.

Vaccination

Table 4 summarizes the recommendations for vaccine use in patients receiving biologics and JAK inhibitors. Studies on the influenza vaccine in patients treated with anti-TNF agents have shown that lower antibody titers do not correlate with reduced seroprotection.⁶⁴ Appropriate immune responses have also been observed in individuals treated with rituximab, abatacept, tocilizumab,^{64,65} secukinumab,^{66,67} and JAK inhibitors.⁶⁸⁻⁷⁰

Similarly, the efficacy and safety of pneumococcal vaccination have been assessed in various populations with autoimmune diseases.^{64,68,71-74} These studies indicate no significant impairment in vaccine response or serious adverse events in patients treated with different biological or syn-

Table 4 – Summary of vaccination recommendations for patients on biological therapies or targeted synthetic antirheumatic drugs.

Recommendation	Level of agreement
20 In patients with inflammatory rheumatic diseases, the rheumatology team should annually assess vaccination status and determine the need for additional vaccinations.	93%
21 The individualized vaccination plan should be explained to the patient by both the rheumatology team and the primary care physician to facilitate shared decision-making.	71%
22 Vaccination in subjects with inflammatory rheumatic diseases should preferably be administered during the inactive phase of the disease.	93%
23 Vaccines should ideally be given before the initiation of immunosuppressive therapy, particularly B-cell depletion therapy, in individuals with inflammatory rheumatic diseases.	93%
24 Non-live vaccines can be safely administered to patients with inflammatory rheumatic diseases who are receiving systemic glucocorticoids or disease-modifying antirheumatic drugs.	93%
25 All subjects receiving biological or targeted synthetic drugs must be vaccinated against influenza and pneumococcus (PPV13, followed by PPSV23 eight weeks later, and a PPSV23 booster after five years).	100%
26 The recombinant herpes zoster vaccine is recommended for all individuals with rheumatic diseases who are over 50 years old or at high risk.	93%
27 If the live attenuated herpes zoster vaccine is used in patients with rheumatic diseases, it should be administered at least one month before starting biological treatment or targeted synthetic antirheumatic drugs.	100%
28 The yellow fever vaccine is not recommended for subjects with rheumatic diseases who are receiving biological or targeted synthetic antirheumatic drugs.	100%
29 The DPT vaccine may be administered to individuals on biological therapy or with targeted synthetic antirheumatic drugs if needed.	93%
30 The HPV vaccine is both effective and safe for women with rheumatic diseases and should be administered according to national guidelines.	100%
31 All patients with rheumatic diseases should receive vaccination against SARS-CoV-2 by the general population's recommendations, maintaining an up-to-date schedule.	100%
32 Some therapies may require modifications to ensure adequate immunogenicity for SARS-CoV-2 vaccination (see Table 5).	100%

thetic targeted antirheumatic drugs, including rituximab, tocilizumab, abatacept, tofacitinib, baricitinib, and upadacitinib. However, long-term studies on the persistence of humoral responses and immunological memory are still lacking.⁷⁵

In contrast, evidence regarding the immunogenicity and safety of herpes zoster (HZ) vaccines in patients with rheumatic diseases suggests that the recombinant vaccine performs better than the live attenuated vaccine, although both vaccines have acceptable efficacy, and a similar rate of serious adverse events compared to the general population.^{76–79} The live attenuated HZ vaccine is more cost-effective in individuals aged 60 to 69 years.⁸⁰

Women with rheumatic diseases who are undergoing immunosuppressive treatment are at higher risk than the general population for human papillomavirus (HPV) infection and subsequent cervical cancer.^{81,82} The quadrivalent HPV vaccine is well tolerated, reasonably effective, and does not appear to increase disease activity.^{83–85} Additionally, evidence suggests

that anti-TNF therapies do not affect seroconversion following vaccination.^{86,87}

Currently, available data on the correlation between antibody titers and immune responses to SARS-CoV-2 vaccines are limited. It is known, however, that the immune response in subjects with autoimmune inflammatory rheumatic diseases receiving systemic immunomodulatory therapies is typically reduced in both magnitude and duration compared to the general population.^{88–92} Aside from known allergies to vaccine components, there are no additional contraindications for COVID-19 vaccination in this patient group, where the benefits of vaccination generally outweigh the risks of new-onset autoimmunity.⁸⁹ To enhance immunogenicity, modification of DMARD treatment around the time of vaccination is recommended^{89,93,94} (Table 5). Finally, individual cases should be assessed in consultation with infectious disease specialists, especially when considering the timing of vaccination about starting biologic therapy or JAK inhibitors. In cases where patients have a history of herpes infection or are on

Table 5 – Considerations for the timing of immunomodulatory therapy and COVID-19 vaccination.

Drug	Considerations
Abatacept (IV) Abatacept (SC)	Schedule vaccination one week before the next dose of abatacept (IV). Discontinue for one to two weeks (as disease activity permits) after each dose of the COVID-19 vaccine.
Belimumab (SC)	Discontinue for one to two weeks (as disease activity permits) after each dose of the COVID-19 vaccine.
Anti-TNF, anti-IL-6, anti-IL-1, anti-IL-17, anti-IL-12/23, anti-IL-23, and other cytokine inhibitors	Previously, it was advised not to modify therapy; however, there is currently no consensus on whether it is appropriate to temporarily interrupt these treatments after each dose of the COVID-19 vaccine, including both primary vaccination and supplementary/booster doses.
Rituximab or other anti-CD20 B-cell depleting agents	Discuss the optimal timing of dosing and vaccination before proceeding. Some providers measure CD19 B-cells to schedule the COVID-19 booster dose and the subsequent rituximab dose. If this is not feasible, administer the supplementary vaccine dose two to four weeks before the next scheduled rituximab dose.
All other conventional and specific immunomodulatory or immunosuppressive drugs (except those mentioned above)	Discontinue for one to two weeks (as disease activity permits) after each dose of the COVID-19 vaccine.
Moderate level of recommendation based on consensus from the American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases: Version 4.	

Table 6 – Management of biologics and other drugs in the perioperative setting for patients with inflammatory rheumatic diseases.

Drug ^a	Dosing interval	Recommended time of surgery after last dose
Infliximab	Every 4, 6, or 8 weeks	Weeks 5, 7, or 9
Adalimumab	Every 2 weeks	Week 3
Etanercept	Every week	Week 2
Abatacept	Monthly (IV) or weekly (SC)	Week 5; Week 2
Certolizumab	Every 2 or 4 weeks	Week 3 or 5
Golimumab	Every 4 weeks (SC) or every 8 weeks (IV)	Week 5 (SC), Week 9 (IV)
Rituximab	Two doses 2 weeks apart, every 4 to 6 months	Month 7
Tocilizumab	Every week (SC) or every 4 weeks (IV)	Week 2; Week 5
Anakinra	Daily	Day 2
Secukinumab	Every 4 weeks	Week 5
Ustekinumab	Every 12 weeks	Week 13
Ixekizumab	Every 4 weeks	Week 5
Guselkumab	Every 8 weeks	Week 9
Tofacitinib	Daily or twice daily (PO)	Day 4
Baricitinib	Daily (PO)	Day 4
Upadacitinib	Daily (PO)	Day 4

Adapted from Goodman et al.¹⁰⁰

SC: Subcutaneous; IV: Intravenous; PO: Oral route.

^a Discontinue these medications before surgery and schedule the last dose at the end of the dosing cycle. Resume medications at least 14 days after surgery, in absence of wound healing problems, surgical site infection, or systemic infection.

high-dose glucocorticoids or other immunosuppressants, the timing of vaccination may need to be adjusted. In all instances, healthcare professionals should carefully review the medication insert for each drug regarding vaccination safety and potential interactions.

Surgery

Evidence from meta-analyses⁹⁵⁻⁹⁹ has reported an increased perioperative risk of infection, and the risk-benefit balance of continuing or discontinuing biologic or targeted synthetic antirheumatic drugs should be carefully considered. The American College of Rheumatology and the American Association of Hip and Knee Surgeons guidelines¹⁰⁰ recommend discontinuing biologic drugs 1 to 13 weeks before surgery,

depending on the half-life of the specific drug (Table 6). Recent meta-analyses have shown a significant increase in post-operative infectious complications in patients on anti-TNF therapy,⁹⁷ recommending that anti-TNF agents be withheld for two half-lives before surgery⁹⁹ and restarted two to three weeks post-surgery, provided wound healing is satisfactory.¹⁰¹

Close monitoring of wound healing and signs of systemic inflammatory response is critical, particularly in emergency surgeries where discontinuation of biologic therapy was not possible. This is especially important in patients with other risk factors for infection, such as increased disease activity, glucocorticoid use, smoking, diabetes,⁹⁹ or a high risk of wound dehiscence.¹⁰² Biologic therapy should be resumed as soon as possible after complete wound healing.^{103,104} Table 7

Table 7 – Summary of recommendations for surgical interventions in patients receiving biological therapies or targeted synthetic antirheumatic drugs.

Recommendation	Level of agreement
33 In patients receiving biological agents or targeted synthetic antirheumatic drugs who are scheduled for surgery, it is recommended to continue the usual dose of the following medications during the procedure: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, or apremilast.	93%
34 For surgical procedures in subjects on biological therapy, it is recommended to suspend one dose and schedule the procedure when the next dose is due (see Table 6).	100%
35 In individuals receiving JAK inhibitors who are scheduled for surgery, it is recommended to discontinue the drug (tofacitinib, baricitinib, or upadacitinib) four days before the procedure.	100%
36 In patients who discontinued treatment before surgery, therapy should be resumed after the procedure, provided there is no evidence of infection and wound healing is satisfactory.	100%
37 In subjects with unscheduled surgeries, where it was not possible to suspend the biological agent or JAK inhibitor, close monitoring for signs of infection and potential healing complications should be conducted.	100%

outlines recommendations for surgical procedures in individuals using biologics or JAK inhibitors.¹⁰⁵

Cardiovascular disease

Several DMARDs, including anti-TNF agents, abatacept, and IL-6 inhibitors, appear to improve various markers of cardiovascular disease¹⁰⁵ (such as significant reductions in leptin and resistin, along with an increase in adiponectin and reduction in the atherogenic and insulin resistance indices) and reduce cardiovascular events in cohort studies of patients with rheumatic diseases.^{106–108} In subjects with atherosclerosis treated with tofacitinib¹⁰⁶ and those with rheumatoid arthritis managed with anti-TNF agents or JAK inhibitors,¹⁰⁹ cohort studies have shown a slight decrease in carotid intima-media thickness. However, it remains unclear whether this improvement is due to a reduction in overall disease activity or to specific atheroprotective effects. Clinical trials with tocilizumab¹¹⁰ and baricitinib¹¹¹ have shown a significant increase in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, with no significant differences in major cardiovascular outcomes. Targeted synthetic antirheumatic drugs may carry a slightly higher risk of thrombotic events than standard therapy in some patients, but the evidence is limited, and long-term clinical studies are needed.¹¹²

Current recommendations for cardiovascular risk screening are based on international guidelines and expert consensus.¹¹³ The panel emphasizes the importance of risk stratification, using the Framingham scale adapted for Colombia, by any physician on the multidisciplinary care team. Individualized decisions should be made to assess and mitigate cardiovascular risk in patients on targeted biological or synthetic therapies (see Table 8).

Pregnancy and breastfeeding

Overall, studies on the long-term effects of targeted biological or synthetic drugs during pregnancy or lactation on child health and development are limited and often of low quality. Therefore, factors specific to the disease—such as treatment indications, drug dosage, disease activity, degree

Table 8 – Summary of recommendations regarding cardiovascular disease in patients receiving biological or targeted synthetic antirheumatic therapies.

Recommendation	Level of agreement
38 All patients with rheumatic diseases should undergo screening for traditional cardiovascular risk factors and further stratification.	93%
39 Subjects identified as having higher-than-expected cardiovascular risk should be referred to the appropriate medical specialty for additional preventive measures.	86%
40 Cardiovascular risk assessment should be conducted at least once every five years for all individuals with rheumatic diseases and re-assessed after significant changes in antirheumatic treatment.	79%

of systemic inflammation, organ involvement, comorbidities, other medications, and the risk of disease flare during pregnancy—must be carefully considered. Drug-related factors, including molecular structure, the likelihood of crossing the placental barrier, exposure duration, and the timing of administration, along with clinically significant and long-term effects on the newborn exposed *in utero*, should also be considered.¹¹⁴ Additionally, factors such as personal experience with a particular drug, its availability in the country, and its teratogenic classification are important considerations.

Studies indicate that women who wish to become pregnant and are on biological therapy do not have higher rates of spontaneous abortion or congenital malformations compared to pregnant women who used biologics before pregnancy.¹¹⁵ The best quality studies assessing safety during pregnancy have been conducted for certain drugs. The highest placental transfer has been reported for infliximab and adalimumab, low for etanercept, and extremely low for certolizumab.^{116,117} Recommendations regarding the timing of drug use during

Table 9 – Summary of recommendations for the use of biological therapies or targeted synthetic antirheumatic drugs during pregnancy and breastfeeding.

Recommendation	Level of agreement
41 Certolizumab is the safest of the biologics and can be used throughout pregnancy.	100%
42 Other options that are permissible during pregnancy include infliximab, adalimumab (up to week 20), or etanercept (up to weeks 30–32). If necessary, these can be used throughout the pregnancy, considering the risk-benefit ratio.	93%
43 Do not use targeted synthetic antirheumatic drugs or biological agents during pregnancy, such as ustekinumab, rituximab, belimumab, secukinumab, or tocilizumab, among others.	86%
44 If the mother continues biological therapy after 22 weeks, live attenuated vaccines (e.g., BCG, rotavirus, oral polio) should be administered to the infant after six months of age. Inactivated vaccines may be administered according to national guidelines.	100%
45 The use of biological therapies is not contraindicated during lactation.	90%

pregnancy are based on evidence of potential associations with adverse fetal events.^{118–121}

Based on available data, maternal use of anti-TNF agents is considered compatible with breastfeeding.¹²² Although data are limited, it is believed that the transfer of these biologics from serum to breast milk is minimal (0.1–1%).^{123,124} Regarding the safety of biologics or targeted synthetic antirheumatic drugs, while the evidence is limited, no risks have been found in infants, so their use during breastfeeding can generally be considered safe.

In all cases, healthcare providers are advised to review the drug insert for specific safety information regarding use during pregnancy and breastfeeding. Table 9 summarizes recommendations for care during these periods.

Immunological consequences

Evidence suggests an association between hypogammaglobulinemia and repeated use of drugs such as rituximab, depending on the cumulative dose.^{125–127} Subsequent rituximab treatments in patients have led to further reductions in immunoglobulin levels, justifying the monitoring of immunoglobulin concentrations and persistent hypogammaglobulinemia.

There is insufficient evidence regarding the measurement of immunoglobulins before initiating rituximab. However, based on clinical immunologists' experience, baseline immunoglobulin G (IgG) measurement is used as a predictor of infection risk, with subsequent measurements to assess the drug's effects. Forty-three percent of the expert panel approved baseline IgG measurement, and 79% recommended its evaluation before each rituximab cycle. This remains a controversial issue; thus, factors such as age, history of recurrent infections, and specific clinical circumstances should guide clinical judgment on the frequency of immunoglobulin testing.

Consensus update

The need to update this consensus should be reassessed in three years or earlier if relevant evidence emerges that alters

the indications. This decision will be subject to ASOREUMA considerations.

Declaration of editorial independence

The updated consensus was developed independently, transparently, and impartially by the development group. Funding entities did not influence on the content or final document.

Financing

This consensus was supported by three unrestricted financial contributions from Janssen Colombia, Novartis Colombia, and Abbvie SAS Colombia.

Conflict of interest

Conflict of interest were declared by all participants at the start of the process, before the expert consensus. Declarations are provided in Supplementary material Appendix A1, Declaration of Interests.

Acknowledgments

We would like to thank the extended panel of experts for their contributions to the discussion and final recommendations: Santiago Bernal Macias (internist, rheumatologist, epidemiology specialist), Juan Carlos Cataño Correa (internist, infectious disease specialist), Jeimmy Andrea Chaparro Sanabria (rheumatologist), Oscar Jair Felipe Díaz (internist, rheumatologist), María Constanza Latorre Muñoz (internist, rheumatologist), Diana Marcela Muñoz Urbano (rheumatologist), Jorge Luis Quinteros Barrios (internist, pulmonologist), Luis Orlando Roa Pérez (internist, rheumatologist, economics specialist), and Wilmer Gerardo Rojas Zuleta (internist, rheumatologist).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.rcreue.2024.11.005>.

REFERENCES

- Patel SV, Khan DA. Adverse reactions to biologic therapy. *Immunol Allergy Clin North Am*. 2017;37:397-412, <http://dx.doi.org/10.1016/j.iac.2017.01.012>.
- Boyman O, Comte D, Spertini F. Adverse reactions to biologic agents and their medical management. *Nat Rev Rheumatol*. 2014;10:612-27, <http://dx.doi.org/10.1038/nrrheum.2014.123>.
- Mayall SJ, Banerjee AK. *Therapeutic risk management of medicines*. Great Britain: Elsevier Science & Technology; 2014. p. 9-23.
- McLornan DP, Pope JE, Gotlib J, Harrison CN. Current and future status of JAK inhibitors. *Lancet*. 2021;398:803-16, [http://dx.doi.org/10.1016/S0140-6736\(21\)00438-4](http://dx.doi.org/10.1016/S0140-6736(21)00438-4).
- Forero E, Chalem M, Vásquez G, Jauregui E, Medina LF, Pinto Peñaranda LF, et al. Gestión de riesgo para la prescripción de terapias biológicas. *Rev Colomb Reumatol*. 2016;23:50-67, <http://dx.doi.org/10.1016/j.rcreu.2016.02.004>.
- Fondo Colombiano de Enfermedades de Alto Costo, Cuenta de Alto Costo (CAC). Situación de la artritis reumatoide en Colombia 2021. Bogotá: Fondo Colombiano de Enfermedades de Alto Costo; 2022 [Accessed 14 January 2023]. Available from: <https://cuentadealtocosto.org/publicaciones/situacion-de-la-artritis-reumatoide-en-colombia-2021/>.
- Liberati A, Altman D, Tetzlaff J, Mulrow C, Gotzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100, <http://dx.doi.org/10.1371/journal.pmed.1000100>.
- Anton C, Machado FD, Ramirez JMA, Bernardi RM, Palominos PE, Brenol CV, et al. Latent tuberculosis infection in patients with rheumatic diseases. *J Bras Pneumol*. 2019;45:e20190023, <http://dx.doi.org/10.1590/1806-3713/e20190023>.
- Kit Ying O'Young C, Ho KM, So H, Yun Wing Mok T, Chiu Leung C, Hung Chau C, et al. Recommendations on management of latent tuberculosis infection in patients initiating anti-tumor necrosis factor biologics. *J Clin Rheumatol Immunol*. 2021;21:51-7, <http://dx.doi.org/10.1142/S2661341721500012>.
- Wang PH, Lin CH, Chang TH, Wu CS. Chest roentgenography is complementary to interferon-gamma release assay in latent tuberculosis infection screening of rheumatic patients. *BMC Pulm Med*. 2020;20:232, <http://dx.doi.org/10.1186/s12890-020-01274-9>.
- Baričević D, Popović Grle S, Morović Vergles J, Čuković Čavka S, Jakopović M, Redžepi G, et al. QuantiFERON-TB gold in-tube test in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists. *Acta Clin Croat*. 2017;56:203-9, <http://dx.doi.org/10.20471/acc.2017.56.02.02>.
- Al-Taweel T, Strohl M, Pai M, Martel M, Bessissow T, Bitton A, et al. A Study of optimal screening for latent tuberculosis in patients with inflammatory bowel disease. *Dig Dis Sci*. 2018;63:2695-702, <http://dx.doi.org/10.1007/s10620-018-5178-1>.
- Koker O, Sahin S, Adrovic A, Yildiz M, Barut K, Gulle B, et al. A controversial topic in juvenile idiopathic arthritis: association between biologic agents and malignancy. *Int J Rheum Dis*. 2020;23:1210-8, <http://dx.doi.org/10.1111/1756-185X.13906>.
- Malaviya A, Thakaran R, Rawat R, Kapoor S, Garg S, Baghel S, et al. Real life experience of a screening strategy for latent tuberculosis before treatment with biologicals in Indian patients with rheumatic diseases. *Indian J Rheumatol*. 2018;13:233-9, <http://dx.doi.org/10.4103/injr.injr.66.18>.
- República de Colombia, Ministerio de Salud y Protección Social. In: Resolución 227 de 2020. Bogotá: Secretaría Jurídica Distrital; 2020. p. 50-8.
- Bautista-Molano W, González L, Fernández-Ávila D, Cardozo R, Ruiz Ó. Frecuencia de positividad de la prueba de intradermorreacción a tuberculina en una cohorte de pacientes con artritis reumatoide. *Biomédica*. 2021;41:472-80, <http://dx.doi.org/10.7705/biomedica.5416>.
- Fragoulis GE, Dey M, Zhao S, Schoones J, Courvoisier D, Galloway J, et al. Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *RMD Open*. 2022;8:e002726, <http://dx.doi.org/10.1136/rmdopen-2022-002726>.
- Cuomo G, D'Arosca V, Iacono D, Pantano I. The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis. *Clin Rheumatol*. 2017;36:457-61, <http://dx.doi.org/10.1007/s10067-016-3462-z>.
- Shimabuco AY, Medeiros-Ribeiro AC, Miossi R, Bonfiglioli KR, Moraes JCB, Gonçalves CR, et al. Ankylosing spondylitis and psoriatic arthritis: revisiting screening of latent tuberculosis infection and its follow-up during anti-tumor necrosis factor therapy in an endemic area. *Clinics (Sao Paulo)*. 2020;75:e1870, <http://dx.doi.org/10.6061/clinics/2020/e1870>.
- Yang QY, Liu YJ, Xu Y, Zhang L, Wang CD. Monitoring frequency of interferon gamma release assay for tuberculosis surveillance following infliximab therapy in patients with Crohn's disease. *J Dig Dis*. 2021;22:473-80, <http://dx.doi.org/10.1111/1751-2980.13032>.
- Goel N, Torralba K, Downey C, Salto L. Screening for acquired latent tuberculosis in rheumatoid arthritis patients on tumor necrosis factor inhibition therapy in Southern California. *Clin Rheumatol*. 2020;39:2291-7, <http://dx.doi.org/10.1007/s10067-020-04991-y>.
- Taxonera C, Ponferrada Á, Riestra S, Bermejo F, Saro C, et al., CONVERT study group from GETECCU. Serial tuberculin skin tests improve the detection of latent tuberculosis infection in patients with inflammatory Bowel disease. *J Crohns Colitis*. 2018;12:1270-9, <http://dx.doi.org/10.1093/ecco-jcc/jjy104>.
- Chaer FGG, de Lucena Valim JM, Reis RC, Klautau GB, de Souza BDB. Use of biologic agents and risk of tuberculosis in Brazil, a tuberculosis high-burden country. *Drugs Context*. 2020;9:212598, <http://dx.doi.org/10.7573/dic.212598>.
- Lai HC, Chang CH, Cheng KS, Chen TW, Tsai YY, Chou JW. QuantiFERON-TB gold test conversion is associated with active tuberculosis development in inflammatory Bowel disease patients treated with biological agents: an experience of a medical center in Taiwan. *Gastroenterol Res Pract*. 2019;2019:7132875, <http://dx.doi.org/10.1155/2019/7132875>.
- Pettipher C, Benitha R. Tuberculosis in biologic users for rheumatic diseases: results from the South African Biologics Registry (SABIO). *Ann Rheum Dis*. 2020;79:292-9, <http://dx.doi.org/10.1136/annrheumdis-2019-216128>.
- Fragoulis GE, Nikiphorou E, Dey M, Zhao SS, Courvoisier DS, Arnaud L, et al. 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in

- adults with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis.* 2023;82:742-53, <http://dx.doi.org/10.1136/ard-2022-223335>.
27. Lopes DMA, Pinheiro VGF, Monteiro HSA. Diagnosis and treatment of latent tuberculosis infection in patients undergoing treatment with immunobiologic agents: a four-year experience in an endemic area. *J Bras Pneumol.* 2019;45:e20180225, <http://dx.doi.org/10.1590/1806-3713/e20180225>.
 28. Handa R, Upadhyaya S, Kapoor S, Jois R, Pandey BD, Bhatnagar AK, et al. Tuberculosis and biologics in rheumatology: a special situation. *Int J Rheum Dis.* 2017;20:1313-25, <http://dx.doi.org/10.1111/1756-185X.13129>.
 29. Akyuz F, Cavus B, Iliaz R, Soyer OM, Ormeci A, Evirgen S, et al. Inflammatory bowel disease and mycobacteria: how much can we trust isoniazid prophylaxis during antitumor necrosis factor therapy? *Eur J Gastroenterol Hepatol.* 2019;31:777-80, <http://dx.doi.org/10.1097/MEG.0000000000001403>.
 30. Goletti D, Petrone L, Ippolito G, Niccoli L, Nannini C, Cantini F. Preventive therapy for tuberculosis in rheumatological patients undergoing therapy with biological drugs. *Expert Rev Anti Infect Ther.* 2018;16:501-12, <http://dx.doi.org/10.1080/14787210.2018.1483238>.
 31. Cantini F, Niccoli L, Capone A, Petrone L, Goletti D. Risk of tuberculosis reactivation associated with traditional disease modifying anti-rheumatic drugs and non-anti-tumor necrosis factor biologics in patients with rheumatic disorders and suggestion for clinical practice. *Expert Opin Drug Saf.* 2019;18:415-25, <http://dx.doi.org/10.1080/14740338.2019.1612872>.
 32. Zhang Z, Fan W, Yang G, Xu Z, Wang J, Cheng Q, et al. Risk of tuberculosis in patients treated with TNF- α antagonists: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open.* 2017;7:e012567, <http://dx.doi.org/10.1136/bmjopen-2016-012567>.
 33. Bernal JA, Andrés M, Jovaní V, García Sevilla R, Begazo A, Vela P. Primoinfección tuberculosa en pacientes con anti-TNF- α y cribado inicial negativo. *Reumatol Clin.* 2016;12:81-4, <http://dx.doi.org/10.1016/j.reuma.2015.04.001>.
 34. Gruss A, Contrera M, Piñeiro N, Perna A, Gambogi R, Alemán A, et al. Incidencia de tuberculosis en pacientes que reciben fármacos anti-TNF α . *Rev Med Uru.* 2020;36:23-43, <http://dx.doi.org/10.29193/RMU.36.1.2>.
 35. Sartori NS, Picon P, Papke A, Neyeloff JL, da Silva Chakr RM. A population-based study of tuberculosis incidence among rheumatic disease patients under anti-TNF treatment. *PLoS One.* 2019;14:e0224963, <http://dx.doi.org/10.1371/journal.pone.0224963>.
 36. Kordzadeh-Kermani E, Khalili H, Karimzadeh I, Salehi M. Prevention strategies to minimize the infection risk associated with biologic and targeted immunomodulators. *Infect Drug Resist.* 2020;13:513-32, <http://dx.doi.org/10.2147/IDR.S233137>.
 37. Godfrey MS, Friedman LN. Tuberculosis and biologic therapies: anti-tumor necrosis factor- α and beyond. *Clin Chest Med.* 2019;40:721-39, <http://dx.doi.org/10.1016/j.ccm.2019.07.003>.
 38. Elewski BE, Baddley JW, Deodhar AA, Magrey M, Rich PA, Soriano ER, et al. Association of secukinumab treatment with tuberculosis reactivation in patients with psoriasis, psoriatic arthritis, or ankylosing spondylitis. *JAMA Dermatol.* 2021;157:43-51, <http://dx.doi.org/10.1001/jamadermatol.2020.3257>.
 39. Kammüller M, Tsai TF, Griffiths CE, Kapoor N, Kolattukudy PE, Brees D, et al. Inhibition of IL-17A by secukinumab shows no evidence of increased Mycobacterium tuberculosis infections. *Clin Transl Immunol.* 2017;6:e152, <http://dx.doi.org/10.1038/cti.2017.34>.
 40. Kelsey A, Chirch LM, Payette MJ. Tuberculosis and interleukin blocking monoclonal antibodies: is there risk? *Dermatol Online J.* 2018;24:1-5, <http://dx.doi.org/10.5070/D3249041425>.
 41. Evangelatos G, Koulouri V, Iliopoulos A, Fragoulis GE. Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors. *Ther Adv Musculoskelet Dis.* 2020;12:1759720X20930116, <http://dx.doi.org/10.1177/1759720X20930116>.
 42. Soare A, Gheorghiu AM, Aramă V, Bumbăcea D, Dobrotă R, Oneață R, et al. Risk of active tuberculosis in patients with inflammatory arthritis receiving TNF inhibitors: a look beyond the baseline tuberculosis screening protocol. *Clin Rheumatol.* 2018;37:2391-7, <http://dx.doi.org/10.1007/s10067-017-3916-y>.
 43. Ramos GP, Stroh G, Al-Bawardy B, Faubion WA, Papadakis KA, Escalante P. Outcomes of treatment for latent tuberculosis infection in patients with inflammatory Bowel disease receiving biologic therapy. *Inflamm Bowel Dis.* 2018;24:2272-7, <http://dx.doi.org/10.1093/ibd/izy133>.
 44. Thi AA, Abbara A, Bouri S, Collin SM, Wolfson P, Owen L, et al. Challenges in screening for latent tuberculosis in inflammatory bowel disease prior to biologic treatment: a UK cohort study. *Frontline Gastroenterol.* 2018;9:234-40, <http://dx.doi.org/10.1136/flgastro-2017-100951>.
 45. Borren NZ, Ananthakrishnan AN. Safety of biologic therapy in older patients with immune-mediated diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2019;17:1736-43.e4, <http://dx.doi.org/10.1016/j.cgh.2018.12.032>.
 46. Hou LQ, Jiang GX, Chen YF, Yang XM, Meng L, Xue M, et al. The comparative safety of TNF inhibitors in ankylosing spondylitis-a meta-analysis update of 14 randomized controlled trials. *Clin Rev Allergy Immunol.* 2018;54:234-43, <http://dx.doi.org/10.1007/s12016-017-8623-6>.
 47. Li J, Zhang Z, Wu X, Zhou J, Meng D, Zhu P. Risk of adverse events after anti-TNF treatment for inflammatory rheumatological disease. A meta-analysis. *Front Pharmacol.* 2021;12:746396, <http://dx.doi.org/10.3389/fphar.2021.746396>.
 48. Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: systematic review, meta-analysis, and network meta-analysis. *Semin Arthritis Rheum.* 2017;47:149-56, <http://dx.doi.org/10.1016/j.semarthrit.2017.02.007>.
 49. Pundole X, Suarez-Almazor ME. Cancer and rheumatoid arthritis. *Rheum Dis Clin North Am.* 2020;46:445-62, <http://dx.doi.org/10.1016/j.rdc.2020.05.003>.
 50. Xie W, Xiao S, Huang Y, Sun X, Gao D, Ji L, et al. A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. *Rheumatology (Oxford).* 2021;60:2495, <http://dx.doi.org/10.1093/rheumatology/keaa871>.
 51. Kim SC, Pawar A, Desai RJ, Solomon DH, Gale S, Bao M, et al. Risk of malignancy associated with use of tocilizumab versus other biologics in patients with rheumatoid arthritis: a multi-database cohort study. *Semin Arthritis Rheum.* 2019;49:222-8, <http://dx.doi.org/10.1016/j.semarthrit.2019.03.002>.
 52. Huss V, Bower H, Wadström H, Frisell T, Askling J, ARTIS group. Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice. *Rheumatology (Oxford).* 2022;61:1810-8, <http://dx.doi.org/10.1093/rheumatology/keab570>.
 53. Mastorino L, Dapavo P, Avallone G, Merli M, Cariti C, Rubatto M, et al. Biologic treatment for psoriasis in cancer patients: should they still be considered forbidden? *J Dermatolog*

- Treat. 2022;33:2495-502, <http://dx.doi.org/10.1080/09546634.2021.1970706>.
54. Castañeda OM, Romero FJ, Salinas A, Citera G, Mysler E, Rillo O, et al. Safety of tofacitinib in the treatment of rheumatoid arthritis in Latin America compared with the rest of the world population. *J Clin Rheumatol*. 2017;23:193-9, <http://dx.doi.org/10.1097/RHU.0000000000000498>.
 55. Fiorentino D, Ho V, Lebwohl MG, Leite L, Hopkins L, Galindo C, et al. Risk of malignancy with systemic psoriasis treatment in the psoriasis longitudinal assessment registry. *J Am Acad Dermatol*. 2017;77:845-54.e5, <http://dx.doi.org/10.1016/j.jaad.2017.07.013>.
 56. Simon TA, Boers M, Hochberg M, Baker N, Skovron ML, Ray N, et al. Comparative risk of malignancies and infections in patients with rheumatoid arthritis initiating abatacept versus other biologics: a multi-database real-world study. *Arthritis Res Ther*. 2019;21:228, <http://dx.doi.org/10.1186/s13075-019-1992-x>.
 57. Abreu C, Sarmento A, Magro F. Screening, prophylaxis and counselling before the start of biological therapies: a practical approach focused on IBD patients. *Dig Liver Dis*. 2017;49:1289-97, <http://dx.doi.org/10.1016/j.dld.2017.09.002>.
 58. Hall SAL, Shaikh A, Teh K, Tantiongco M, Coghlan D, Karapetis CS, et al. Hepatitis B screening before rituximab therapy: a multicentre South Australian study of adherence. *Intern Med J*. 2018;48:936-43, <http://dx.doi.org/10.1111/imj.13740>.
 59. Drößler L, Lehmann C, Töpel K, Nierhoff D, Vehreschild JJ, Rybníček J, et al. HBsAg-negative/anti-HBc-positive patients treated with rituximab: prophylaxis or monitoring to prevent hepatitis B reactivation? *Infection*. 2019;47:293-300, <http://dx.doi.org/10.1007/s15010-019-01271-z>.
 60. Lopetuso LR, Mocci G, Marzo M, D'Aversa F, Rapaccini GL, Guidi L, et al. Harmful effects and potential benefits of anti-tumor necrosis factor (TNF)- α on the liver. *Int J Mol Sci*. 2018;19:2199, <http://dx.doi.org/10.3390/ijms19082199>.
 61. Magri S, Chessa L, Demurtas M, Cabras F, Mocci G. Review article: safety of new biologic agents for inflammatory bowel disease in the liver. *Eur J Gastroenterol Hepatol*. 2021;33:623-30, <http://dx.doi.org/10.1097/MEG.0000000000002076>.
 62. Harigai M, Winthrop K, Takeuchi T, Hsieh TY, Chen YM, Smolen JS, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open*. 2020;6:e001095, <http://dx.doi.org/10.1136/rmdopen-2019-001095>.
 63. Kuo MH, Tseng CW, Lu MC, Tung CH, Tseng KC, Huang KY, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing tocilizumab-containing treatment. *Dig Dis Sci*. 2021;66:4026-34, <http://dx.doi.org/10.1007/s10620-020-06725-1>.
 64. Subesinghe S, Bechman K, Rutherford AI, Goldblatt D, Galloway JB. A Systematic review and metaanalysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. *J Rheumatol*. 2018;45:733-44, <http://dx.doi.org/10.3899/jrheum.170710>.
 65. Richi P, Martín MD, Navío MT, González-Hombrado L, Salido M, Llorente J, et al. Antibody responses to influenza vaccine in patients on biological therapy: results of RIER cohort study. *Med Clin*. 2019;153:380-6, <http://dx.doi.org/10.1016/j.medcli.2019.02.003>.
 66. Furer V, Zisman D, Kaufman I, Arad U, Berman M, Sarbagil-Maman H, et al. Immunogenicity and safety of vaccination against seasonal influenza vaccine in patients with psoriatic arthritis treated with secukinumab. *Vaccine*. 2020;38:847-51, <http://dx.doi.org/10.1016/j.vaccine.2019.10.081>.
 67. Richi P, Martín MD, de Ory F, Gutiérrez-Larraya R, Casas I, Jiménez-Díaz AM, et al. Secukinumab does not impair the immunogenic response to the influenza vaccine in patients. *RMD Open*. 2019;5:e001018, <http://dx.doi.org/10.1136/rmdopen-2019-001018>.
 68. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687-95, <http://dx.doi.org/10.1136/annrheumdis-2014-207191>.
 69. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79:39-52, <http://dx.doi.org/10.1136/annrheumdis-2019-215882>.
 70. Colmegna I, Useche ML, Rodriguez K, McCormack D, Alfonso G, Patel A, et al. Immunogenicity and safety of high-dose versus standard-dose inactivated influenza vaccine in rheumatoid arthritis patients: a randomised, double-blind, active-comparator trial. *Lancet Rheumatol*. 2020;2:e14-23, [http://dx.doi.org/10.1016/S2665-9913\(19\)30094-3](http://dx.doi.org/10.1016/S2665-9913(19)30094-3).
 71. Adawi M, Bragazzi NL, McGonagle D, Watad S, Mahroum N, Damiani G, et al. Immunogenicity, safety and tolerability of anti-pneumococcal vaccination in systemic lupus erythematosus patients: an evidence-informed and PRISMA compliant systematic review and meta-analysis. *Autoimmun Rev*. 2019;18:73-92, <http://dx.doi.org/10.1016/j.autrev.2018.08.002>.
 72. van Aalst M, Langedijk AC, Spijker R, de Bree GJ, Grobusch MP, Goorhuis A. The effect of immunosuppressive agents on immunogenicity of pneumococcal vaccination: asystematic review and meta-analysis. *Vaccine*. 2018;36:5832-45, <http://dx.doi.org/10.1016/j.vaccine.2018.07.039>.
 73. Berho J, Monsalvez MP, Rojas J, Inostroza J, Quezada A. Pneumococcal vaccine in patients with idiopathic juvenile arthritis in treatment with tumor necrosis factor inhibitors. *Allergol Immunopathol (Madr)*. 2021;49:149-54, <http://dx.doi.org/10.15586/aei.v49i4.203>.
 74. Winthrop KL, Bingham CO 3rd, Komocsar WJ, Bradley J, Issa M, Klar R, et al. Evaluation of pneumococcal and tetanus vaccine responses in patients with rheumatoid arthritis receiving baricitinib: results from a long-term extension trial substudy. *Arthritis Res Ther*. 2019;21:102, <http://dx.doi.org/10.1186/s13075-019-1883-1>.
 75. Nived P, Jönsson G, Settergren B, Einarsson J, Olofsson T, Jørgensen CS, et al. Prime-boost vaccination strategy enhances immunogenicity compared to single pneumococcal conjugate vaccination in patients receiving conventional DMARDs, to some extent in abatacept but not in rituximab-treated patients. *Arthritis Res Ther*. 2020;22:36, <http://dx.doi.org/10.1186/s13075-020-2124-3>.
 76. Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. *Arthritis Rheumatol*. 2017;69:1969-77, <http://dx.doi.org/10.1002/art.40187>.
 77. Calabrese LH, Abud-Mendoza C, Lindsey SM, Lee SH, Tatulich S, Takiya L, et al. Live zoster vaccine in patients with rheumatoid arthritis treated with tofacitinib with or without methotrexate, or adalimumab with methotrexate: a post hoc analysis of data from a phase IIIb/IV randomized study. *Arthritis Care Res (Hoboken)*. 2020;72:353-9, <http://dx.doi.org/10.1002/acr.24010>.
 78. Curtis J, Cofield S, Bassler J. Results from a randomized controlled trial of the safety of the live varicella vaccine in TNF-treated patients. *Arthritis Rheumatol*. 2019;71.

79. Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Bühler S. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - a systematic review of randomized trials, observational studies and case reports. *Vaccine*. 2017;35:1216-26, <http://dx.doi.org/10.1016/j.vaccine.2017.01.048>.
80. Gómez Rincón JC, Munive AA, Cano Gutierrez CA, Coral Alvarado PX, Coronell Rodríguez W, et al. Guías para la inmunización del adolescente y adulto en Colombia. Documento de actualización, 2016. *Infectio*. 2016;20:192-210, <http://dx.doi.org/10.1016/j.infect.2016.08.001>.
81. Kim SC, Glynn RJ, Giovannucci E, Hernández-Díaz S, Liu J, Feldman S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. *Ann Rheum Dis*. 2015;74:1360-7, <http://dx.doi.org/10.1136/annrheumdis-2013-204993>.
82. Zard E, Arnaud L, Mathian A, Chakhtoura Z, Hie M, Touraine P, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: a meta-analysis of the literature. *Autoimmun Rev*. 2014;13:730-5, <http://dx.doi.org/10.1016/j.autrev.2014.03.001>.
83. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis*. 2013;72:659-64, <http://dx.doi.org/10.1136/annrheumdis-2012-201393>.
84. Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol RJ. The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus. *Vaccine*. 2017;35:2642-6, <http://dx.doi.org/10.1186/1546-0096-11-29>.
85. Infante V, Miyaji KT, Soarez PC, Sartori AMC. Systematic review and meta-analysis of HPV vaccination in women with systemic lupus erythematosus (SLE). *Expert Rev Vaccines*. 2021;20:309-18, <http://dx.doi.org/10.1080/14760584.2021.1889375>.
86. Pellegrino P, Radice S, Clementi E. Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune diseases: a systematic review. *Vaccine*. 2015;33:3444-9, <http://dx.doi.org/10.1016/j.vaccine.2015.05.041>.
87. Heijstek MW, Scherpenisse M, Groot N, Tacke C, Schepp RM, Buisman AM, et al. Immunogenicity and safety of the bivalent HPV vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study. *Ann Rheum Dis*. 2014;73:1500-7, <http://dx.doi.org/10.1136/annrheumdis-2013-203429>.
88. Fagni F, Simon D, Tascilar K, Schoenau V, Sticherling M, Neurath MF, et al. COVID-19 and immune-mediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses. *Lancet Rheumatol*. 2021;3:e724-36, [http://dx.doi.org/10.1016/S2665-9913\(21\)00247-2](http://dx.doi.org/10.1016/S2665-9913(21)00247-2).
89. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American College of Rheumatology Guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 4. *Arthritis Rheumatol*. 2022;74:e21-36, <http://dx.doi.org/10.1002/art.4210>.
90. Jena A, Mishra S, Deepak P, Kumar-M P, Sharma A, Patel YI, et al. Response to SARS-CoV-2 vaccination in immune mediated inflammatory diseases: systematic review and meta-analysis. *Autoimmun Rev*. 2022;21:102927, <http://dx.doi.org/10.1016/j.autrev.2021.102927>.
91. Friedman MA, Curtis JR, Winthrop KL. Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80:1255-65, <http://dx.doi.org/10.1136/annrheumdis-2021-221244>.
92. Medeiros-Ribeiro AC, Bonfiglioli KR, Domiciano DS, Shimabuco AY, da Silva HC, Saad CGS, et al. Distinct impact of DMARD combination and monotherapy in immunogenicity of an inactivated SARS-CoV-2 vaccine in rheumatoid arthritis. *Ann Rheum Dis*. 2022;81:710-9, <http://dx.doi.org/10.1136/annrheumdis-2021-221735>.
93. Park JK, Lee EB, Shin K, Sung YK, Kim TH, Kwon SR, et al. COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: clinical guidance of the Korean College of Rheumatology. *J Korean Med Sci*. 2021;36:e95, <http://dx.doi.org/10.3346/jkms.2021.36.e95>.
94. Santosa A, Xu C, Arkachaisri T, Kong KO, Lateef A, Lee TH, et al. Recommendations for COVID-19 vaccination in people with rheumatic disease: developed by the Singapore Chapter of Rheumatologists. *Int J Rheum Dis*. 2021;24:746-57, <http://dx.doi.org/10.1111/1756-185X.14107>.
95. Qiu Y, Zheng Z, Liu G, Zhao X, He A. Effects of preoperative anti-tumour necrosis factor alpha infusion timing on postoperative surgical site infection in inflammatory bowel disease: a systematic review and meta-analysis. *United European Gastroenterol J*. 2019;7:1198-214, <http://dx.doi.org/10.1177/2050640619878998>.
96. Xu Y, Yang L, An P, Zhou B, Liu G. Meta-analysis: the influence of preoperative infliximab use on postoperative complications of Crohn's disease. *Inflamm Bowel Dis*. 2019;25:261-9, <http://dx.doi.org/10.1093/ibd/izy246>.
97. Law CC, Bell C, Koh D, Bao Y, Jairath V, Narula N. Risk of postoperative infectious complications from medical therapies in inflammatory bowel disease. *Cochrane Database Syst Rev*. 2020;10:CD013256, <http://dx.doi.org/10.1002/14651858.CD013256>.
98. Del Olmo L, Hernández B, Galindo-Izquierdo M, Tébar D, Balsa A, Carmona L. Manejo perioperatorio de los fármacos modificadores de la enfermedad en Reumatología: recomendaciones basadas en un metaanálisis [Peri-operative management of disease modifying anti-rheumatic drugs: recommendations based on a meta-analysis]. *Rev Esp Cir Ortop Traumatol*. 2012;56:393-412, <http://dx.doi.org/10.1016/j.recot.2012.05.001>.
99. Goodman SM, Menon I, Christos PJ, Smethurst R, Bykerk VP. Management of perioperative tumour necrosis factor α inhibitors in rheumatoid arthritis patients undergoing arthroplasty: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2016;55:573-82, <http://dx.doi.org/10.1093/rheumatology/kev364>.
100. Goodman SM, Springer BD, Chen AF, Davis M, Fernandez DR, Figgie M, et al. 2022 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. *Arthritis Care Res (Hoboken)*. 2022;74:1399-408, <http://dx.doi.org/10.1002/acr.24893>.
101. Goodman SM. Optimizing perioperative outcomes for older patients with rheumatoid arthritis undergoing arthroplasty: emphasis on medication management. *Drugs Aging*. 2015;32:361-9, <http://dx.doi.org/10.1007/s40266-015-0262-0>.
102. Mege D, Michelassi F. Is anti-TNF therapy associated with an increased risk of postoperative morbidity after surgery for ileocolonic Crohn disease? *Ann Surg*. 2018;267:229-30, <http://dx.doi.org/10.1097/SLA.0000000000002586>.
103. Albrecht K, Poddubnyy D, Leipe J, Sewerin P, Iking-Konert C, Scholz R, et al. Perioperative management of patients with

- inflammatory rheumatic diseases: updated recommendations of the German Society for Rheumatology. *Z Rheumatol.* 2023;82 Suppl 1:1–11, <http://dx.doi.org/10.1007/s00393-021-01150-9>.
104. Lightner AL, Grass F, Alsughayer AM, Harmsen WS, Petersen M, Loftus EV Jr. Are biologics safe in the immediate postoperative period? A single-center evaluation of consecutive Crohn's surgical patients. *Dis Colon Rectum.* 2020;63:934–43, <http://dx.doi.org/10.1097/DCR.0000000000001649>.
 105. Corrado A, Colia R, Rotondo C, Sanpaolo E, Cantatore FP. Changes in serum adipokines profile and insulin resistance in patients with rheumatoid arthritis treated with anti-TNF- α . *Curr Med Res Opin.* 2019;35:2197–205, <http://dx.doi.org/10.1080/03007995.2019.1654988>.
 106. Atzeni F, Rodríguez-Carrio J, Popa CD, Nurmohamed MT, Szűcs G, Szekanecz Z. Cardiovascular effects of approved drugs for rheumatoid arthritis. *Nat Rev Rheumatol.* 2021;17:270–90, <http://dx.doi.org/10.1038/s41584-021-00593-3>.
 107. Day AL, Singh JA. Cardiovascular disease risk in older adults and elderly patients with rheumatoid arthritis: what role can disease-modifying antirheumatic drugs play in cardiovascular risk reduction? *Drugs Aging.* 2019;36:493–510, <http://dx.doi.org/10.1007/s40266-019-00653-0>.
 108. Atzeni F, Nucera V, Galloway J, Zoltán S, Nurmohamed M. Cardiovascular risk in ankylosing spondylitis and the effect of anti-TNF drugs: a narrative review. *Expert Opin Biol Ther.* 2020;20:517–24, <http://dx.doi.org/10.1080/14712598.2020.1704727>.
 109. Rojas-Giménez M, López-Medina C, Calvo-Gutiérrez J, Puche-Larrubia MÁ, Gómez-García I, Seguí-Azpilcueta P, et al. Association between carotid intima-media thickness and the use of biological or small molecule therapies in patients with rheumatoid arthritis. *Diagnostics (Basel).* 2021;12:64, <http://dx.doi.org/10.3390/diagnostics12010064>.
 110. Gladman DD, Charles-Schoeman C, McInnes IB, Veale DJ, Thiers B, Nurmohamed M, et al. Changes in lipid levels and incidence of cardiovascular events following tofacitinib treatment in patients with psoriatic arthritis: a pooled analysis across phase III and long-term extension studies. *Arthritis Care Res (Hoboken).* 2019;71:1387–95, <http://dx.doi.org/10.1002/acr.23930>.
 111. Ytterberg SR, Bhatt DL, Connell CA. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *Reply. N Engl J Med.* 2022;386:1768, <http://dx.doi.org/10.1056/NEJMc2202778>.
 112. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med.* 2022;386:316–26, <http://dx.doi.org/10.1056/NEJMoa2109927>.
 113. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis.* 2017;76:17–28, <http://dx.doi.org/10.1136/annrheumdis-2016-209775>.
 114. Soh MC, Moretto M. The use of biologics for autoimmune rheumatic diseases in fertility and pregnancy. *Obstet Med.* 2020;13:5–13, <http://dx.doi.org/10.1177/1753495X19841799>.
 115. Ghalandari N, Dolhain RJEM, Hazes JMW, van Puijenbroek EP, Kapur M, Crijns HJM. Intrauterine exposure to biologics in inflammatory autoimmune diseases: a systematic review. *Drugs.* 2020;80:1699–722, <http://dx.doi.org/10.1007/s40265-020-01376-y>.
 116. Paizis K. Immunomodulatory drugs in pregnancy and lactation. *Aust Prescr.* 2019;42:97–101, <http://dx.doi.org/10.18773/austprescr.2019.026>.
 117. Ponticelli C, Moroni G. Fetal toxicity of immunosuppressive drugs in pregnancy. *J Clin Med.* 2018;7:552, <http://dx.doi.org/10.3390/jcm7120552>.
 118. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016;75:795–810, <http://dx.doi.org/10.1136/annrheumdis-2015-208840>.
 119. Chambers CD, Johnson DL, Xu R, Luo Y, Lopez-Jimenez J, Adam MP, et al. Birth outcomes in women who have taken adalimumab in pregnancy: a prospective cohort study. *PLoS One.* 2019;14:e0223603, <http://dx.doi.org/10.1371/journal.pone.0223603>.
 120. Eworuke E, Panucci G, Goulding M, Neuner R, Toh S. Use of tumor necrosis factor-alpha inhibitors during pregnancy among women who delivered live born infants. *Pharmacoepidemiol Drug Saf.* 2019;28:296–304, <http://dx.doi.org/10.1002/pds.4695>.
 121. Geldhof A, Slater J, Clark M, Chandran U, Coppola D. Exposure to infliximab during pregnancy: post-marketing experience. *Drug Saf.* 2020;43:147–61, <http://dx.doi.org/10.1007/s40264-019-00881-8>.
 122. De Felice KM, Kane S. Safety of anti-TNF agents in pregnancy. *J Allergy Clin Immunol.* 2021;148:661–7, <http://dx.doi.org/10.1016/j.jaci.2021.07.005>.
 123. Góralczyk A, Kolossa K, Waszczak-Jeka M, Adamczak R, Jeka S. The exposure to biologic and targeted synthetic disease-modifying antirheumatic drugs in pregnancy and lactation. *Postepy Dermatol Alergol.* 2020;37:306–12, <http://dx.doi.org/10.5114/ada.2020.96294>.
 124. Ghalandari N, Dolhain RJEM, Hazes JMW, Siezen CLE, van der Laan JW, Crijns HJM, et al. The pre- and post-authorisation data published by the European medicines agency on the use of biologics during pregnancy and lactation. *Br J Clin Pharmacol.* 2020;86:580–90, <http://dx.doi.org/10.1111/bcp.14145>.
 125. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis.* 2016;75:1583–94, <http://dx.doi.org/10.1136/annrheumdis-2016-209133>.
 126. Padoan R, Felicetti M, Gatto M, Polito P, Doria A, Schiavon F. Rituximab-associated hypogammaglobulinaemia in ANCA-associated vasculitis and connective tissue diseases: a longitudinal observational study. *Clin Exp Rheumatol.* 2020;38 Suppl 124:188–94.
 127. Wade SD, Kyttaris VC. Rituximab-associated hypogammaglobulinemia in autoimmune rheumatic diseases: a single-center retrospective cohort study. *Rheumatol Int.* 2021;41:1115–24, <http://dx.doi.org/10.1007/s00296-021-04847-x>.