



## Original Article

## Consensus Statement of the Spanish Society of Rheumatology on Risk Management of Biologic Therapy in Rheumatic Patients<sup>☆</sup>

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## ARTICLE INFO

## Article history:

Received 1 March 2011

Accepted 4 May 2011

## Keywords:

Rheumatic diseases

Risk management

Consensus

Recommendations

Guidelines

Biologic therapy

Systemic autoimmune diseases

## ABSTRACT

**Objective:** Due to the increasing use of biologic therapy in rheumatic diseases and the importance of its risk management, the Spanish Society of Rheumatology (SER) has promoted the development of recommendations based on the best evidence available. These recommendations should be a reference to rheumatologists and those involved in the treatment of patients who are using, or about to use biologic therapy irrespectively of the rheumatic disease.

**Methods:** Recommendations were developed following a nominal group methodology and based on systematic reviews. The level of evidence and degree of recommendation were classified according to the model proposed by the Center for Evidence Based Medicine at Oxford. The level of agreement was established through a Delphi technique. Evidence from previous consensus and clinical guidelines was used.

**Results:** We have produced recommendations on risk management of biologic therapy in rheumatic patients. These recommendations include indication risk management, risk management before the use of biologic therapy, risk management during follow-up, attitude to adverse events, and attitude to special situations.

**Conclusions:** We present the SER recommendations related to biologic therapy risk management.

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<sup>☆</sup> Please cite this article as: Gómez Reino J, et al. Consenso SER sobre la gestión de riesgo del tratamiento con terapias biológicas en pacientes con enfermedades reumáticas. Reumatol Clin. 2011, doi:10.1016/j.reuma.2011.05.002.

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## Consenso SER sobre la gestión de riesgo del tratamiento con terapias biológicas en pacientes con enfermedades reumáticas

### R E S U M E N

#### Palabras clave:

Enfermedades reumáticas  
Gestión del riesgo  
Consenso  
Recomendaciones  
Guía  
Terapia biológica  
Enfermedades autoinmunes sistémicas

**Objetivo:** Dado el creciente uso de las terapias biológicas en distintas enfermedades reumatológicas, y la importancia de la gestión de riesgo de las mismas, desde la Sociedad Española de Reumatología (SER) se ha impulsado el desarrollo de recomendaciones basadas en la mejor evidencia posible. Estas deben de servir de referencia para reumatólogos e implicados en el tratamiento de pacientes en tratamiento o en los que se quiere indicar la terapia biológica independientemente de su enfermedad de base.

**Métodos:** Las recomendaciones se emitieron siguiendo la metodología de grupos nominales. El nivel de evidencia y el grado de recomendación se clasificaron según el modelo del *Center for Evidence Based Medicine* de Oxford y el grado de acuerdo se extrajo por técnica Delphi. Se utilizó toda la información de consensos y guías de práctica clínica previas.

**Resultados:** Se realizan recomendaciones sobre la gestión del riesgo del uso de las terapias biológicas en pacientes con enfermedades reumática. Incluyen la gestión del riesgo de la indicación, gestión del riesgo antes de iniciar el tratamiento, gestión del riesgo durante el seguimiento, actitud ante acontecimientos adversos, y actitud en situaciones especiales.

**Conclusiones:** Se presentan las recomendaciones SER sobre la gestión del riesgo del tratamiento con terapias biológicas.

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### Introduction

The objective of this paper is to develop recommendations on risk management of biological therapies in patients with rheumatic diseases, regardless of their underlying disease.

Biological therapies are, according to the European Drug Agency, intended for use in treating diseases; the drugs are produced by biotechnology methods, mainly cultured cells from cell banks, with the exception of microbial metabolites, such as antibiotics, amino acids, carbohydrates and other substances of low molecular weight. These therapies are designed to act specifically on an important therapeutic target crucial to the pathogenic process of disease.

There are currently several biologic therapies approved in Spain (Table 1) with indications for rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and osteoporosis (OP). They include infliximab (IFX), etanercept (ETN), adalimumab (ADA), anakinra, abatacept (ABT), rituximab (RTX), tocilizumab (TCZ), certolizumab (CZP), golimumab, denosumab, teriparatide and rh-PTH 1–84.

Because denosumab, teriparatide and rh-PTH 1–84 have a mechanism of action and safety profile very different from other biological therapies here presented, and considering that are discussed in detail in the 2011 consensus document on osteoporosis, this consensus will only provide basic data on them. For more information the reader is referred to the BE 2011 consensus on osteoporosis.

Finally, we must note that this document has been written with the intent to provide guidance for all professionals who at one time may use biological therapies to treat patients with rheumatic diseases.

### Methods

This consensus has been developed from other SER consensus documents related to the management of biological therapies in RA,<sup>1</sup> SA, PsA, as well as clinical practice guidelines GUIPCAR<sup>2</sup> and ESPOGUA,<sup>3</sup> and other publications of scientific interest.<sup>4–6</sup> It was considered that the risk management of patients on biological therapies is a section that is repeated in various published documents, and is also subject to the variability of the expert panel that prepared it. This variability may lead to contradictory attitudes, so it was considered appropriate to produce a single consensus document that reflects how the risks of using biological therapy should be managed.

Under this premise, a panel of expert rheumatologists who participated in the publication of guidelines and/or consensus previously mentioned was created. Then, all of the previous recommendations of the various documents were collected, modified or updated (if considered appropriate). Subsequently, through a secret ballot, the degree of agreement (DA) for each of the recommendations was obtained. The aggregate results of this vote were shown to all the panelists (Delphi modified). The recommendations showing an agreement of less than 70% were re-edited and voted on in a second round.

The level of evidence (LE) and the degree of recommendation (DR) of each recommendation was set according to the model of the Center for Evidence Based Medicine of Oxford<sup>7</sup> by members of the research unit of the SER.

### Preliminary Considerations

#### Pharmacovigilance and Risk Management

Risk management in the use of medications is an important part of pharmacovigilance. This may be defined, in turn, as the activity of public health whose objectives are the identification, quantification, assessment and prevention drug related risks once they are marketed, as collected in the royal decree (RD) 1344/2007.

More specifically, risk management represents the set of pharmacovigilance activities and interventions designed to identify, characterize and prevent or minimize the risks of drugs and evaluate the effectiveness of such interventions. It is everyone's responsibility, regulatory agencies/health authorities, pharmaceutical companies, researchers, health professionals, etc. to work on all.

In recent years, with the use of biological therapies we have identified a number of risks more or less associated with them. Some are identified as significant, that is, those where there is adequate evidence of association with the drug and are very relevant. Other potential risks are important, meaning there are grounds for suspicion, but no confirmation. On the other hand, it should be pointed out that we currently do not have enough relevant information in specific cases, such as in so-called special situations (pregnancy, nursing, etc.).

Based on the above, the management of risk in relation to the use of biologic therapy is present at the following times/circumstances (discussed throughout the document): indication, start of treatment, monitoring and in the assessment of adverse events arising

**Table 1**  
Biologic therapies approved in Spain and their characteristics (according to their data sheet).<sup>a</sup>

Active Ingredient	Structure and Mechanism of Action	Dosage and Administration	Indications	Contraindications	Adverse Events <sup>b</sup>
Abatacept	<ul style="list-style-type: none"> <li>- Fusion protein formed by the extracellular domain of cytotoxic T lymphocyte antigen 4 (CTLA-4) and a modified fragment of human IgG1</li> <li>- Inhibits binding of CD28 with CD80 blocking T lymphocyte costimulation</li> </ul>	<ul style="list-style-type: none"> <li>- Dose (according to body weight): &lt;60 kg: 500 mg 60–100 kg: 750 mg &gt;100 kg: 1.000 mg</li> <li>- 30 min IV infusion</li> <li>- Frec: after the first dose, repeat at 2 and 4 weeks, then every 4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe RA in combination with MTX (except when contraindicated) after an inadequate response or intolerance to <math>\geq 1</math> DMARD including MTX or a TNF antagonist</li> <li>- Moderate to severe active JIA in combination with MTX, in <math>\geq 6</math> years with failure to DMARD including at least one TNF antagonist</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to the main ingredient or drug components</li> <li>- Severe and uncontrolled infections</li> </ul>	<ul style="list-style-type: none"> <li>- Very frequent.: headache, skin rash</li> <li>- Frequent.: nausea, herpes, respiratory/urinary infection</li> <li>- Less frequent.: skin cancer, cytopenia, psoriasis</li> <li>- Rare: septicemia</li> </ul>
Adalimumab	<ul style="list-style-type: none"> <li>- Recombinant human monoclonal antibody</li> <li>- TNF<math>\alpha</math> blocker</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 40 mg</li> <li>- Subcutaneous</li> <li>- Freq.: every two weeks. May be administered once a week if lack of response is seen to normal dose</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe RA in combination with MTX (except when contraindicated) after inadequate response or DMARD including MTX</li> <li>- Active, progressive, severe RA, without prior use of MTX</li> <li>- Active severe SA not responding to conventional therapy</li> <li>- Active, severe PsA with failure to DMARD</li> <li>- Active JIA in combination with MTX, patients (13–17 years) with insufficient response to <math>\geq 1</math> DMARD, and when MTX use is restricted</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient or components</li> <li>- Active TB, severe infections</li> <li>- Moderate to severe HF (NYHA class III/IV)</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: injection site reaction (pain, erythema)</li> <li>- Freq.: headache, herpes, respiratory/urinary infection, diarrhea</li> <li>- Less freq.: SLE, arrhythmia, cytopenia, TB, sepsis</li> <li>- Rare: HF, multiple sclerosis, lymphoma, solid malignant tumor</li> </ul>
Anakinra	<ul style="list-style-type: none"> <li>- Recombinant non glycosylated molecule, a version of IL-1RA</li> <li>- Blocks IL-1 activity by competitively inhibiting binding to IL-1RI</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 100 mg</li> <li>- Subcutaneous</li> <li>- Freq.: daily. Preferable to administrate at the same hour</li> </ul>	<ul style="list-style-type: none"> <li>- RA in combination with MTX in patients not responding to MTX monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient or components or proteins derived from <i>E. coli</i></li> <li>- Severe RI (CrCl &lt;30 ml/min)</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: injection site reaction, headache</li> <li>- Freq.: neutropenia, severe infection</li> </ul>
CertolizumabPegol	<ul style="list-style-type: none"> <li>- Fab' fragment of a recombinant humanized antibody joined to polyethilene glycol</li> <li>- TNF<math>\alpha</math> blocker</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 200 mg</li> <li>- Subcutaneous</li> <li>- Freq.: weeks 0 (2 iny), 2 and 4, then every two weeks</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe active RA in combination with MTX (except when contraindicated) after inadequate response/intolerance to DMARD including MTX</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient, components</li> <li>- Active TB, severe infections</li> <li>- Moderate to severe HF (NYHA class III/IV)</li> </ul>	<ul style="list-style-type: none"> <li>- Freq.: bacterial/viral infection, leukopenia, headache, hypertension, hepatitis, exanthema, injection site reaction, pain, fatigue, fever</li> <li>- Less freq.: TB, solid tumors, non melanoma skin cancer, SLE</li> <li>- Rare: lymphoma, pneumonitis</li> <li>- Freq.: pain in the extremities, respiratory and urinary tract infection, cataracts, constipation, skin rash</li> <li>- Less freq.: diverticulitis, cellulitis, ear infection, eczema,</li> <li>- Rare: hypocalcemia</li> </ul>
Denosumab	<ul style="list-style-type: none"> <li>- Human monoclonal IgG2 antibody</li> <li>- Neutralizes the ligand of the nuclear factor <math>\kappa</math>B ligand (RANKL) blocking its binding to RANK and inhibiting the formation, activation and survival of osteoclasts</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 60 mg</li> <li>- Subcutaneous</li> <li>- Freq: 6 months</li> </ul>	<ul style="list-style-type: none"> <li>- OP in postmenopausal women with <math>\uparrow</math> risk of fracture</li> <li>- Hormonal suppression associated bone loss in men a prostate cancer with <math>\uparrow</math> risk of fractures</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient or components</li> <li>- Hypocalcemia</li> <li>- Pregnancy and nursing</li> </ul>	<ul style="list-style-type: none"> <li>- Freq.: pain in the extremities, respiratory and urinary tract infection, cataracts, constipation, skin rash</li> <li>- Less freq.: diverticulitis, cellulitis, ear infection, eczema,</li> <li>- Rare: hypocalcemia</li> </ul>

Etanercept	<ul style="list-style-type: none"> <li>- Human recombinant fusion protein composed by the p75 receptor of tumor necrosis factor and the Fc of human IgG1</li> <li>- TNF<math>\alpha</math> receptor block</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 25 mg or 50 mg</li> <li>- Subcutaneous</li> <li>- Freq.: 25 mg twice a week (interval of 72–96 h); 50 mg once a week</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe active RA in combination with MTX (except when contraindicated) after inadequate response or intolerance to other DMARD including MTX</li> <li>- Active, progressive severe RA, with no prior use of MTX</li> <li>- Active severe SA with inadequate response to conventional therapy</li> <li>- Active, progressive PsA with inadequate response to DMARD</li> <li>- Active JIA &gt;4 years or teenagers with inadequate response to MTX</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to the active ingredient or components</li> <li>- Sepsis or risk of sepsis</li> <li>- Active infections</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: injection site reaction, respiratory, urinary, skin infection</li> <li>- Freq.: allergy, antibodies</li> <li>- Less freq.: psoriasis, severe infection, thrombocytopenia</li> <li>- Rare: pancytopenia, TB, SLE</li> </ul>
Golimumab	<ul style="list-style-type: none"> <li>- Recombinant human monoclonal IgG1 antibody</li> <li>- TNF<math>\alpha</math> blocker</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 50 mg</li> <li>- Subcutaneous</li> <li>- Freq.: once a month. Try to administer on same day</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe active RA in combination with MTX after inadequate response or intolerance to other DMARD including MTX</li> <li>- Active severe SA with inadequate response to conventional treatment convencional</li> <li>- Active progressive PsA with inadequate response to DMARD, with or without MTX</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient, components</li> <li>- Active TB, severe infections</li> <li>- Moderate to severe HF (NYHA class III/IV)</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: upper respiratory tract infection</li> <li>- Freq.: anemia, allergy, depression, fatigue, hypertension, headache</li> <li>- Less freq.: neoplasia, <math>\uparrow</math> lipids, HF, demyelinating process,</li> <li>- Rare: pancytopenia, lymphoma, reactivation of hepatitis B</li> </ul>
Infliximab	<ul style="list-style-type: none"> <li>- Chimeric human-murine recombinant monoclonal IgG1 antibody</li> <li>- TNF<math>\alpha</math> blocker</li> </ul>	<ul style="list-style-type: none"> <li>- Dose (according to body weight and disease): 3–5 mg/kg</li> <li>- IV infusion over 2 h</li> <li>- Freq.: after first dose, then 2 and 6 weeks. Then every 8 weeks. Dose may <math>\uparrow</math> to 7.5 mg/kg/8 weeks or interval may shorten to 4–6 weeks if ineffective or relapse</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe active RA in combination with MTX (except when contraindicated) after inadequate response or intolerance to other DMARD including MTX</li> <li>- Severe active RA without prior MTX use or other DMARD</li> <li>- Active, severe SA in adults with inadequate response to conventional treatment in combination with MTX or monotherapy if contraindicated/intolerance</li> <li>- Active, progressive PsA with inadequate response to DMARD in combination with MTX or monotherapy if contraindicated/intolerance</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient, components or other murine proteins</li> <li>- Active TB severe infections</li> <li>- Moderate to severe HF (NYHA class III/IV)</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: infusional reaction</li> <li>- Freq.: herpes, headache, respiratory infection, diarrhea</li> <li>- Less freq.: cytopenia, SLE, TB, sepsis</li> <li>- Rare: HF, multiple sclerosis, lymphoma</li> </ul>

Table 1 (Continued)

Active Ingredient	Structure and Mechanism of Action	Dosage and Administration	Indications	Contraindications	Adverse Events <sup>b</sup>
Rituximab	<ul style="list-style-type: none"> <li>- Human murine chimeric recombinant monoclonal IgG1 antibody</li> <li>- Depletion of CD 20 positive lymphocytes</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 1000 mg</li> <li>- Intravenous. 100 mg iv of methylprednisolone (or equivalent) is recommended 30 min before infusion</li> <li>- Freq.: 2nd infusion at 2 weeks, repeat cycle every 6–12 months</li> </ul>	<ul style="list-style-type: none"> <li>- Severe active RA in combination with MTX (except when contraindicated) after inadequate response or DMARD intolerance including one or more TNF blocker</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient or components</li> <li>- Severe active infection</li> <li>- Severe HF (NYHA class IV) or uncontrolled heart disease</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: mild infusional reaction, upper airway infection</li> <li>- Freq.: migraine, urinary tract infection, hypercholesterolemia, paresthesia</li> <li>- Less freq.: severe infusional reactions, severe infections</li> <li>- Rare: severe cardiac disease</li> </ul>
Teriparatide	<ul style="list-style-type: none"> <li>- Active fragment (1–34) of human endogenous parathyroid hormone</li> <li>- Stimulates osteoblasts, indirect ↑ intestinal absorption of calcium and ↑ in renal tubular absorption of calcium and phosphate excretion</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 20 µg</li> <li>- Subcutaneous</li> <li>- Freq.: daily</li> </ul>	<ul style="list-style-type: none"> <li>- OP in postmenopausal women and men with ↑ of the risk of fracture</li> <li>- OP secondary to steroid use in women and men with ↑ of fracture</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to ingredients or components</li> <li>- Pregnancy and nursing</li> <li>- Preexisting hypercalcemia</li> <li>- Severe renal insufficiency</li> <li>- Bone metabolic disease other than OP induced by steroids</li> <li>- Unexplained ↑ of PA</li> <li>- History of external radiation or radiotherapy on bone</li> <li>- Tumors/bone metastasis</li> <li>- Allergy to parathyroid hormone/ingredients</li> <li>- Pregnancy and nursing</li> <li>- Preexisting hypercalcemia and other alterations of calcium and phosphate</li> <li>- Metabolic bone disease other than OP</li> <li>- Unexplained ↑ of PA</li> <li>- History of external radiation or radiotherapy on bone</li> <li>- Severe liver or kidney failure</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: pain in extremities</li> <li>- Freq.: palpitations, dizziness, anemia, paresthesia, cyatica, vertigo, dyspnea, gastro esophageal reflux, fatigue, chest pain, hypercholesterolemia, injection site reaction, headache,</li> <li>- Less freq.: Tachycardia, ↑ weight, heart murmur, ↑ AP, emphysema, hemorrhoids, muscle and joint pain, hypercalcemia &gt;2.76 mmol/L, hyperuricemia</li> <li>- Very freq.: hypercalcemia, hypercalciuria, nausea</li> <li>- Freq.: headache, dizziness, palpitations, injection site erythema, fatigue, vomit, constipation, diarrhea, pain on the extremities, paresthesia</li> <li>- Less freq.: ↑ AP, disgeusia, parosmia, abdominal pain, hyperuricemia, anorexia</li> </ul>
Parathyroid hormone	<ul style="list-style-type: none"> <li>- Parathyroid hormone elaborated using a strain of <i>Escherichia coli</i> modified through recombinant DNA</li> <li>- Stimulates osteoblasts, indirect ↑ in intestinal absorption of calcium and ↑ in tubular renal absorption of calcium and phosphate excretion</li> </ul>	<ul style="list-style-type: none"> <li>- Dose: 100 µg</li> <li>- Subcutaneous</li> <li>- Freq.: daily</li> </ul>	<ul style="list-style-type: none"> <li>- OP in postmenopausal women with ↑ of the risk of fracture</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to parathyroid hormone/ingredients</li> <li>- Pregnancy and nursing</li> <li>- Preexisting hypercalcemia and other alterations of calcium and phosphate</li> <li>- Metabolic bone disease other than OP</li> <li>- Unexplained ↑ of PA</li> <li>- History of external radiation or radiotherapy on bone</li> <li>- Severe liver or kidney failure</li> </ul>	<ul style="list-style-type: none"> <li>- Very freq.: hypercalcemia, hypercalciuria, nausea</li> <li>- Freq.: headache, dizziness, palpitations, injection site erythema, fatigue, vomit, constipation, diarrhea, pain on the extremities, paresthesia</li> <li>- Less freq.: ↑ AP, disgeusia, parosmia, abdominal pain, hyperuricemia, anorexia</li> </ul>
Tocilizumab	<ul style="list-style-type: none"> <li>- Human recombinant monoclonal IgG1 antibody</li> <li>- IL-6 receptor blockage</li> </ul>	<ul style="list-style-type: none"> <li>- Dose (calculated according to weight): 8 mg/kg (no less than 480 mg). Dose adjustment if liver enzyme abnormalities, low neutrophil or platelet count</li> <li>- Intravenous</li> <li>- Freq.: every 4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>- Moderate to severe active RA in combination with MTX (except contraindicated) after inadequate response or intolerance to DMARD or with TNF blockers</li> </ul>	<ul style="list-style-type: none"> <li>- Allergy to active ingredient or components</li> <li>- Severe active infections</li> </ul>	<ul style="list-style-type: none"> <li>- Ver freq.: upper respiratory infection</li> <li>- Freq.: hypercholesterolemia, herpes, elevation of transaminases, HTA, neutropenia</li> <li>- Less freq.: hypertriglyceridemia, elevation of total bilirrubin</li> </ul>

RA: rheumatoid arthritis; JIA: idiopathic arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; AP: alkalyne phosphatase; DMARD: disease modifying anti rheumatic drug; HTA: hypertensin; HF: heart failure; CHF: congestive heart failure; RI: renal insufficiency; iv: intravenous; kg: kilogram; SLE: systemic lupus erythematosus; mg: milligram; MTX: methotrexate; NYHA: New York Heart Association; OP: osteoporosis; TB: tuberculosis; TNF: tumor necrosis factor.

<sup>a</sup> Data on this table has been obtained from the data sheet of the Spanish Drug Agency.

<sup>b</sup> Adverse events: very frequent (at least once every 10 patients); frequent (at least once every 100 patients); less frequents (at least once every 1000 and less than once every 100); rare (at least once every 10000 and less than once every 1000 patients).

during treatment. In most of these times/circumstances, there is evidence on the best conduct to take.

#### *Regulatory Framework in the Use of Drugs in Spain*

Finally, remember the legal framework in which we live. The RD 1345/2007 regulates the authorized use of a drug, and RD 1015/2009 the use of medication in special situations. All documentation is accessible on the website of the Spanish Agency for Drugs and Health Products (AEMPS).<sup>8</sup>

#### *Approved Drugs*

Medications may be used for a condition for which there is an authorized indication (normal use, indication sheet).

#### *Drugs in Special Situations*

*Use of investigational drugs.* AEMPS can authorize the use of investigational drugs prior to marketing in Spain to individual patients without a satisfactory therapeutic alternative available, those who are not part of a clinical trial and are in a clinical situation that cannot wait for the end of the research and new treatments are permitted. So access to these drugs may be requested individually for a patient, as is done until now (compassionate use), or benefiting from temporary authorization for use by AEMPS for a group of patients.

*Use of Drugs For Conditions Other Than Those Authorized.* It refers to the use of the drugs for an unlicensed indication (off-label use or outside the authorized conditions of use). This use is the responsibility of the prescribing physician for individual use, but AEMPS, if considering it appropriate, could regulate its use for that unlicensed indication. In that case, the recommendations for use, or nonuse, would prove enforceable.

*Foreign drugs.* AEMPS may authorize the use of individual drugs that are not allowed in Spain, which are marketed in other countries and whose use is essential.

#### *Risk Management an Indication of Biological Therapy*

The estimated benefit/risk to an individual patient should be based on all available knowledge from the moment of indication. Therefore:

The panel believes that treatment with biologic therapies must be performed by physicians experienced with them and accustomed to managing the diseases for which they are indicated (LE 5, DR D, DA 100%).

Please refer to the official sheet of all biological agents and comply with its recommendations prior to their use in clinical practice (LE 5, DR D, DA 91%).

There is evidence that off-label uses may be linked to more adverse events than when a drug regimen has been approved for such an indication, and the patient to whom it is prescribed must be as close as possible to the profiled indication.<sup>9</sup>

It should be remembered that the indication of biologic therapy for patients with a history of uveitis is not currently authorized; therefore, this would constitute an unlicensed indication. In this context the physician should weigh the relative risks derived from the different drugs and consult an ophthalmologist before deciding on whether to start treatment with biologic therapies and if so, which.<sup>10,11</sup>

A summary of the data sheets of biological therapies is shown in Table 1.

#### *Management of Risk Before Starting Treatment*

Every patient who starts treatment with biologic therapy should undergo a preliminary assessment to detect and/or prevent potential risks and should be monitored regularly during therapy (LE 5, DR D, DA 100%).

Before starting the first dose, the physician should have gathered enough information about potential risks of the individual patient who has been prescribed the medication. To do so, we advise a series of screening or screening measures destined to look for comorbidity, but also suggest proactive measures to minimize the possible adverse reactions, such as providing good information to patients and staff who will manage the therapy and prophylaxis.

Patient monitoring should be regular and adapted to the characteristics of the patient and department organization, with at least one evaluation recommended per month and then every 1–4 months, regardless of who performs it and how it is performed.

Whenever starting a treatment with biological therapy the patient should be instructed about the warning signs to watch for as possible indicators of risk (LE 5, DR D, DA 91%).

When prescribing biologic therapy, regardless of the disease, the patient should be instructed about symptoms/signs to look for and what to do if they occur. The patient should know and recognize these risks; at least the most frequent ones. Similarly, the physician may indicate lifestyle modifications that help reduce some risks. All this information is available in many rheumatology units or the SER<sup>12</sup> website.

The physician who has indicated the drug or one who has been designated for such a purpose should direct the management of risks of treatment with biologic therapies; however, this should involve all of the healthcare staff, including nurses, family physicians, hospital pharmacy and the patient (LE 5, DR D, DA 100%).

The information of the prescribing physician, the one monitoring (if other) and the nurse, must be consistent, for which it is essential to have the support of written documentation, defined processes and clear and precise procedures, brochures, instruction manuals, etc.

In Table 2, the pre-assessment activities recommended at the onset of treatment. Although the safety profile is not identical with different biological therapy options with the information currently available, and except for denosumab, teriparatide and rh-PTH 1–84, the panel considers that the recommendations that follow are applicable to all patients who will undergo biological therapy.

In a patient who's going to start biological treatment, assess the possible existence of an active infection; the presence of the same is a contraindication of biologic therapy (LE 2b, DR B, DA 96%).

The Spanish registry of adverse reactions to biological therapies (BIOBADASER) and other records and/or studies have found an increased incidence of infections in patients with these therapies, regardless of baseline disease.<sup>13–28</sup>

The use of biological therapies in patients with a history of recurrent infections, sepsis or at high risk of developing an infection, is unreliable and requires appropriate risk-benefit balance and maximum surveillance. Nor should physicians begin treatment with these drugs if there is an active, systemic or localized infection. In this sense, the history of an infected prosthetic joint forces the performance, before the start of biological therapy, of the appropriate therapeutic approach (surgery with radical removal of the infection and, if indicated, the prosthetic replacement).

With a growing immigrant population, and according to their geographical origin, it is recommended that the possible reactivation of unusual infections in our environment be evaluated.

Upon resolution of infection, biological therapy can initiate.

The panel considers it necessary to exclude, in any patient about to undergo biological therapy, the existence of active tuberculosis or recent contact with patients with TB and investigate

**Table 2**  
Pretreatment Action and Monitoring of Biologic Therapy.

Active Ingredient	Pre-treatment	During Treatment	Suspension of Treatment
Anti-TNF $\alpha$ Adalimumab Etanercept Infliximab Certolizumab Golimumab	1) Clinical aspects - Rule out: active infection (including TB), cancer, HF, cytopenia, demyelinating disease, relevant comorbidity - Rule out recent contact with TB patients - Unencourage pregnancy 2) Complementary testing: - Hemogram, blood chemistry - HBV, HCV serology - Chest x ray - Mantoux and Booster 3) Other actions: - Antipneumococcal and anti flu vaccine - Evaluate HBV, antimeningococcus, <i>Haemophilus</i> vaccine according to disease or comorbidity - Evaluate antiviral treatment if HBV positive - Avoid vaccines with live or attenuated microorganisms	1) Clinical aspects - Appearance of infections (including TB), severe cytopenia, demyelinating disease, optic neuritis, cancer - Appearance or worsening of HF and lung disease 2) Complementary testing: - Hemogram and blood chemistry every month the first 3 months, then every 3–4 months 3) Other actions: - Depending on patient progression	- Appearance of cancer, demyelinating disease, optic neuritis, severe cytopenia, new interstitial lung disease or worsening of existing, other severe events related to the drug - Temporary suspension if infection or elective major surgery for perioperative period - Evaluate pregnancy and nursing on case by case basis
Anakinra	1) Clinical aspects - Rule out: active infection (including TB), cancer, HF, cytopenia, demyelinating disease, relevant comorbidity - Rule out recent contact with TB patients - Unencourage pregnancy 2) Complementary testing: - Hemogram, blood chemistry - HBV, HCV serology - Chest x ray - Mantoux and Booster 3) Other actions: - Antipneumococcal and anti flu vaccine - Evaluate HBV, antimeningococcus, <i>Haemophilus</i> vaccine according to disease or comorbidity - Avoid vaccines with live or attenuated microorganisms	1) Clinical aspects - Appearance of infections (including TB), severe cytopenia, demyelinating disease, optic neuritis, cancer 2) Complementary testing: - Hemogram and blood chemistry every month the first 3 months, then every 3–4 months 3) Other actions: - Depending on patient progression	- Appearance of cancer, demyelinating disease, optic neuritis, severe cytopenia, other severe events related to the drug - Temporary suspension if infection or elective major surgery for perioperative period - Evaluate pregnancy and nursing on case by case basis
Abatacept	1) Clinical aspects - Rule out: active infection (including TB), cancer, HF, cytopenia, demyelinating disease, relevant comorbidity - Rule out recent contact with TB patients - Unencourage pregnancy 2) Complementary testing: - Hemogram, blood chemistry - HBV, HCV serology - Chest x ray - Mantoux and Booster 3) Other actions: - Antipneumococcal and anti flu vaccine - Evaluate HBV, antimeningococcus, <i>Haemophilus</i> vaccine according to disease or comorbidity - Avoid vaccines with live or attenuated microorganisms	1) Clinical aspects - Appearance of infections (including TB), severe cytopenia, demyelinating disease, optic neuritis, cancer - Appearance or worsening of COPD 2) Complementary testing: - Hemogram and blood chemistry every month the first 3 months, then every 3–4 months 3) Other actions: - Depending on patient progression	- Appearance of cancer, demyelinating disease, optic neuritis, severe cytopenia, respiratory disease or worsening of existing, other severe events related to the drug - Temporary suspension if infection or elective major surgery for perioperative period - Evaluate pregnancy and nursing on case by case basis

Table 2 (Continued)

Active Ingredient	Pre-treatment	During Treatment	Suspension of Treatment
Rituximab	1) Clinical aspects - Rule out: active infection (including TB), cancer, HF, cytopenia, demyelinating disease, relevant comorbidity - Rule out recent contact with TB patients - Unencourage pregnancy 2) Complementary testing: - Hemogram, blood chemistry - HBV, HCV serology, viral replication if positive serology Niveles de inmunoglobulinas Immunoglobulin titers - Chest X ray - Mantoux and Booster 3) Other actions: - Antipneumococcal and anti flu vaccine - Evaluate HBV, HCV, viral load if serology positive, Immunoglobulin levels, antimeningococcus, <i>Haemophilus</i> vaccine according to disease or comorbidity - Evaluate antiviral treatment if HBV positive - Avoid vaccines with live or attenuated microorganisms	1) Clinical aspects - Appearance of infections (including TB), severe cytopenia, demyelinating disease, optic neuritis, cancer - Appearance or worsening of neurologic disease 2) Complementary testing: - Hemogram and blood chemistry every month the first 3 months, then every 3–4 months 3) Other actions: - Depending on patient progression	- Appearance of cancer, cytopenia, other severe events related to the drug - Temporary suspension if infection or elective major surgery for perioperative period - Evaluate pregnancy and nursing on case by case basis
Tocilizumab	1) Clinical aspects - Rule out: active infection (including TB), cancer, HF, cytopenia, demyelinating disease, relevant comorbidity - Rule out recent contact with TB patients - Unencourage pregnancy 2) Complementary testing: - Hemogram, blood chemistry - HBV, HCV serology - Chest X ray - Mantoux and Booster 3) Other actions: - Antipneumococcal and anti flu vaccine - Evaluate HBV, antimeningococcus, <i>Haemophilus</i> vaccine according to disease or comorbidity - Avoid vaccines with live or attenuated microorganisms	1) Clinical aspects - Appearance of infections (including TB), severe cytopenia, demyelinating disease, optic neuritis, cancer, diverticulitis 2) Complementary testing: - Hemogram and blood chemistry, lipids every month the first 3 months, then every 3–4 months 3) Other actions: - Depending on patient progression	- Appearance of cancer, demyelinating disease, optic neuritis, severe cytopenia, other severe events related to the drug - Temporary suspension if infection or elective major surgery for perioperative period - Evaluate pregnancy and nursing on case by case basis

COPD: chronic obstructive pulmonary disease; HF: heart failure; RX: simple X ray; TB: tuberculosis; HBV: hepatitis B virus; HCV: hepatitis C virus.

the possibility of latent tuberculosis infection. It is important to register, in the medical history, any recent contact with TB and TB patients and perform a chest radiograph to rule out active TB or radiographic evidence consistent with an old TB infection, as well as perform a TB skin test (PPD), which must be repeated (re-test) at 1–2 weeks if <5 mm (LE 2b, DR B, DA 100%).

A higher incidence of tuberculosis (TB) has been detected in patients receiving TNF antagonists, particularly monoclonal antibodies.<sup>5,23,24,29–31</sup> Furthermore, screening has been associated with reduced risk of reactivation of latent TB.<sup>5,32</sup> PPD is considered positive in a re-test or in a patient undergoing immunosuppression with an induration greater than or equal than 5 mm at 72 h. The result should be considered regardless of previous vaccination for tuberculosis. It is also important to educate patients about the risks associated with exposure to patients with active TB.

Treatment should be instituted for latent tuberculosis infection before starting biological therapy in the following circumstances: (1) recent contact with a patient with documented TB, (2) a

history of partially treated TB, (3) or positive PPD test or re-test; (4) residual lesions in the chest radiograph. The pattern of choice for treatment of latent tuberculosis infection is isoniazid (5 mg/kg/day up to 300 mg daily) with vitamin B6 for 9 months (LE 2b, DR B, 96 DA%).

In case of intolerance to isoniazid, rifampicin is recommended in doses of 10 mg/kg/day (maximum, 600 mg daily) for four months. The effectiveness of these guidelines to prevent reactivation of latent TB has been demonstrated.<sup>32</sup> Studies of short treatment courses are emerging<sup>33</sup> with various drugs, although we are awaiting confirmation of their efficacy in immunosuppressed patients.

If the patient has received adequate treatment for latent TB infection, active prophylaxis or Mantoux testing is not necessary (LE 5, DRD, DA 96%). However, monitoring is recommended in such patients.

Before starting a biological treatment, the physician must take into account the history of malignancies. When there is a strong history of cancer, its biology and behavior should be assessed,



discussing with the oncologist and the patient the risk of recurrence. We do not recommend the use of biologic therapy in patients with a history of lymphoproliferative disease (LE 4, DR C, DA 91%).

There is no current evidence of increased risk of solid tumors in patients undergoing biological therapy<sup>18,34,35</sup> although there seems to be an increased risk in relation to non-melanocytic skin tumors (basal), at least in patients with RA.<sup>36</sup> Therefore, in patients with a history of solid tumors, indication of biological therapy will be settled on its risks and benefits.

On the other hand, there are conflicting data regarding the risk of developing lymphoproliferative disease with the use of TNF antagonists (see data sheets) in RA,<sup>37–41</sup> and there seems to be an association in SA.<sup>42</sup> While this issue is not definitively clear, we discourage the use of TNF antagonists if there is a history of lymphoproliferative disease.

Before starting biological treatment, patients should be evaluated for heart failure (LE 4, DR C, DA 91%).

Although the available data (relative to TNF antagonists and RTX) are not entirely consistent<sup>43–45</sup> in patients with mild heart failure, patients should be monitored and discontinuation of treatment carried out in case of worsening heart failure. Do not initiate treatment in patients with a NYHA functional class III or IV.

In general, biological therapy should be individualized for in patients with underlying interstitial lung disease (No. 4, GR C, GA 96%).

The use of biological therapies in patients with interstitial lung disease may be associated with a risk (although little studied and defined) of worsening or fatal outcome.<sup>46,47</sup> This risk may be increased in patients with prior history of lung disease, and the worst outcomes have been reported in patients with usual interstitial pneumonitis, so one should pay particular attention to this information.<sup>46,47</sup> Pending more evidence about its use, treatment in these patients should be individualized.

Before starting biological treatment, assess the existence of cytopenias, and do not start treatment with until they are resolved (LE 2b, DR B, DA 74%).

In cases of severe cytopenia, it is not recommended to start treatment until resolved. On the other hand, since cytopenia may be due to the activity of the underlying disease their origin should be studied and acted upon accordingly.

Before starting a biological treatment, assess the existence of demyelinating disease and avoid treating patients with a clear history of such processes (LE 2b, DR B, DA 91%).

There have been reports of demyelinating disease with the use of TNF antagonists<sup>48–50</sup> and there is, according to their data sheet, a potential risk with TCZ and ABT, although it is unclear whether the use of these drugs actually increases the risk of it. This screening may be done clinically and if in doubt, consultation with a neurologist or specialist performed. In case of prior demyelinating disease, indication of biological therapy should be evaluated individually in the light of its risks and benefits, but generally should be avoided.

Serology marker detection is recommended for HCV and HBV (LE 4, DR C, DA 100%).

In patients with HBV and receiving TNF antagonists cases of reactivation of infection and even liver failure have been reported.<sup>51–53</sup> There is no data on reactivation<sup>54</sup> regarding the use of RTX. In the case of HCV, it is not clear whether treatment with TNF antagonists or the use of ABT brings about a deterioration of liver function or increased viral load and improvement has even been described in some functional tests.<sup>55–59</sup> The case of RTX is not clear.<sup>60,61</sup> In connection with the human immunodeficiency virus (HIV), there are series of cases in which biological agents have been effective, but which have also shown an increase in infections.<sup>62</sup> Therefore, we believe that each case must be individualized and the risk/benefit ratio assessed. And, especially in the case of HBV, we recommend a preliminary joint assessment

by the hepatologist/infectious disease specialist for monitoring the risk of reactivation and evaluating the decision for initiation and maintenance of antiviral drugs.

The following vaccines are recommended for patients undergoing biological therapy: pneumococcal vaccine and influenza vaccine (LE 3b, DR C, DA 96%).

On the other hand, using live attenuated vaccines is contraindicated. Given the degree of immunosuppression induced by biological therapy, the potential risk of infection with their prescription may be important, and their use is discouraged.

In principle, if no other risk factors are present, other vaccines may be prescribed. More information on vaccines may be found in [Table 3](#).

In patients with negative markers for hepatitis B, vaccination is recommended prior to initiation of biological therapy (LE 3b, DR C, DA 78%).

In reference to vaccines, several publications have shown a good humoral response in the case of TNF antagonists and ABT for microorganisms such as the influenza virus, pneumococcus or tetanus toxin,<sup>63–66</sup> but is so far contradictory for RTX.<sup>67,68</sup> There is insufficient information in relation to other drugs.

In any case, always take into account that these vaccines may be ineffective if the patient undergoes an intense immunosuppression. After initiation of therapy, biological vaccines containing live bacteria should not be used. For more information see [Table 3](#).

Pregnancy and breast-feeding should be discouraged for patients who will initiate biologic therapy; the use of denosumab is contraindicated in pregnancy and lactation (LE 3b, DR C, DA 91%).

In general, although there is not enough evidence,<sup>69–71</sup> the use of biological therapy during pregnancy and lactation should be discouraged. It is essential that patients and their doctors discuss the pregnancy planning in relation to the use of these therapeutic agents.

#### *Risk Management During Follow-up*

During drug exposure, time intervals for a systematic monitoring of specific events should be established as regularly as possible (LE 5, DR D, DA 100%).

Risk management during treatment with biologic therapies and clinical evaluation includes physical examination and laboratory tests (laboratory, imaging, etc.) depending on each drug and clinical situation (LE 5, DR D, DA 91%).

Treatment should be followed in collaboration and communication with the primary care physician (NE 5, GR D GA 96%).

Close and systematic monitoring has been shown to minimize the adverse effects of any drug. Indeed, close monitoring is standard in clinical trials and adverse effects occur less often. Any means to facilitate communication between primary care and the controller, including the patient with any of these, leads to an expected positive impact on patient safety.

During follow-up special emphasis should be placed on screening for adverse events, especially infections, lung disease, heart failure, as well as on specific cases of laboratory abnormalities (blood alterations, lipids, liver function) as well as monitoring for contact with infectious patients (tuberculosis or chickenpox among others) (LE 5, DR D, DA 96%).

For more details on the management of risk during treatment with biological therapy refer to [Tables 1 and 2](#).

It is advisable to closely monitor patients with active infection with HBV, HCV or HIV if they initiate biologic therapy (LE 5; DR B, DA 100%).

Although the evidence is still scarce,<sup>51,55–58,62</sup> if the physician finally decides to initiate biologic therapy in patients with HBV, HCV or HIV, monitoring should include at least: serology, viral load, CD4

**Table 3**  
Main Characteristics of Some of the Vaccines Available in Spain and Their Recommendations for Use in Patients Undergoing Biologic Therapy.

Vaccine	Microbiologic Classification	Active Ingredient	Recommendation*
Varicella	Live attenuated microorganism	Attenuated varicella virus, Oka strain	Contraindicated
Mumps, measles, rubeolla	Live attenuated microorganism	Attenuated mumps virus, attenuated rubeolla virus, attenuated measles virus	Contraindicated
Yellow fever	Live attenuated microorganism	Yellow fever virus, 17D-2004 strain	Contraindicated
Typhoid fever	Live attenuated microorganism	Attenuated <i>Salmonella typhi</i> , Ty21a strain	Contraindicated
	Simple polysaccharide	<i>Salmonella typhi</i> , PSC Vi	Possible
Polyomelitis	Inactivated microorganisms	Inactivated poliovirus 1,2,3	Possible
Influenza	Fractioned microorganisms	Fractioned (V) influenza virus	Recommended
	Subunits	H and N surface antigens of v influenza virus	
Influenza A (H1N1)	Subunits	Surface antigens of influenza virus	Possible
Haemophilus influenza B	Conjugated	PRP-TT	Possible
Hepatitis A	Inactivated microorganisms	Inactivated hepatitis A virus	Possible
	Virosomes	Inactivated hepatitis A virus	
Hepatitis B	Recombinant	Recombinant HBsAg	Recommended
Human papillomavirus (VPH)	Recombinant	L1 proteins of HPV	Possible
Meningococcus C	Conjugated	PSC of-O-acetylated MC	Possible
Pneumococcus	Simple polysaccharide	PSC pneumococo 23-V	Recommended
	Conjugated	Pneumococcal saccarides-CRM197	
	Conjugated	Protein D, PSC pneumococcus	
Diphtheria	Toxoid	Adult type diphtheric toxoid	Possible
Tetanus	Toxoid	Tetanus toxoid	Possible
Whooping cough	Toxoid	Pertussis toxoid	Possible

count and liver function test. In the case of HBV the use of antiviral therapy should be assessed and, in the case of HIV, biologic therapy should always be associated with intense antiretroviral therapy (which should begin before the start of treatment). As discussed above, we recommend consulting a specialist if in doubt.

#### Attitude to Adverse Events

The physician should pay particular attention to the possible development of infections during treatment. In this situation, diagnosis and treatment of cases, and the temporary removal of biological therapy are essential. Once the infection resolved, treatment may be restarted (LE 2b, DR B, DA 100%).

Infections are the most frequent events. They may occasionally be complex and/or serious, and it is essential to always suspect their presence.<sup>13,20,29,72–76</sup> There have been cases of diverticulitis with intestinal perforation reported using TCZ,<sup>77</sup> so all patients with clinical symptoms of acute abdomen/subacute should be assessed for this possibility.

During follow-up it is recommended to inquire about the possibility of contact with TB patients. If positive or uncertain, repeat the TB skin test or treat exposure with isoniazid (LE 5, DR D, DA 91%).

Even when pretreatment screening or pharmacological prophylaxis has been performed for tuberculosis, the possibility of TB infection still exists, so it is necessary to consider this possibility to follow up and act accordingly.

The QuantiFERON test is an in vitro immune-based rapid assay measuring IFN- $\gamma$  production by circulating mononuclear cells in response to antigens and is more specific for the detection of tuberculosis infection than PPD. Its use in patients with immune-mediated inflammatory diseases has shown a strong correlation with risk factors for tuberculosis and a low percentage of indeterminate results. However, more studies are needed to assess its use in patients treated with TNF<sup>78</sup> antagonists.

There is no evidence that supports a minimum timeframe required for treatment of tuberculosis before initiating biological therapy. Clinical experience makes it advisable to administer it for the longest possible time, always keeping the patients disease activity reasonably low.

If the patient develops cancer during treatment with a biological agent, it should be discontinued (LE 2b, DR B, DA 96%).

Special attention should be paid to the detection of malignant neoplasms.<sup>36,39,42,79–82</sup> Among other situations, clinical suspicion should be established when a mismatch is detected between the clinical symptoms and serum levels of acute phase reactants, the leukocyte count or hemoglobin concentration.<sup>83</sup>

It is also advisable that the patient be explained the importance of observing and reporting any changes in the skin.

The physician should be particularly careful with TNF antagonists and RTX in patients with heart failure, as this condition may worsen considerably, in which case the drug should be discontinued (LE 4, DR C, DA 91%).

Although it requires further evidencia,<sup>43,44</sup> in case there is clinical and/or ultrasound evidence of worsening heart failure, medication should be discontinued.

In patients with interstitial lung disease treated with biologic therapy, clinical and lung function should be strictly controlled, and in cases of clinical worsening and extension of lesions, biological therapy should be abandoned (LE 4; DR C, DA 96%).

There have been reports of worsening interstitial lung disease with fatal outcome in patients treated with TNF antagonists,<sup>46,47</sup> although recently it has been reported that mortality in patients with RA and interstitial lung disease increases with TNF antagonists compared with traditional DMARDs. The proportion of deaths attributable to interstitial lung disease is higher in patients treated with TNF antagonists, although there may be an information bias.<sup>84</sup> This is a little studied subject, in which the cause/effect relationship is poorly defined, so while waiting for more evidence on it, the risk/benefit should be assessed individually.

In case of severe cytopenia during treatment with biologic therapy, this should be discontinued and a search for other possible causes should be explored before attributing it to biological therapy. Once this question has been settled, it may be restored (LE 4, DR C, DA 96%).

There have been rare cases of severe leukopenia or thrombocytopenia and aplastic anemia in patients receiving biologic therapy<sup>85</sup>; in the event of this happening and if it is due to these drugs, stopping the drug until resolved and assessing its reintroduction is mandatory. Due to its mechanism of action, RTX can cause lymphopenia, which would not (per se) be a reason for suspension. In the case of TZC, cytopenia occurs frequently because of a pharmacodynamic effect and management recommendations exist (in literature and its data sheet). On the other hand, anemia, leukopenia, lymphopenia or thrombocytopenia may result from the disease

**Table 4**  
Evidence and Recommendations on the Use of Biologic Therapy During Pregnancy and Nursing.

Drug	Teratogen. (Evidence)*	Fetal toxicity, pregnant, parturition and newborn	Nursing and neonatal	Data sheet recommendations (AEMyPS)
Anti TNF- $\alpha$	B	- Insufficient data in humans - VACTERL syndrome suggested	- Insufficient data in humans	- IFX: • Not recommended during pregnancy • Fertile women must use effective contraception and continue use at least 6 months after last IFX treatment • No nursing for at least 6 months after last IFX treatment -ETN: • Not recommended during pregnancy or nursing • Fertile women must be advised not to become pregnant -Adalimumab: • Not recommended during pregnancy • Fertile women must use effective contraception and must continue treatment for at least 5 months after last IFX treatment • No nursing for at least 5 months after last ADA treatment -Certolizumab pegol: • No concrete position -Golimumab: • Not recommended during pregnancy, only if strictly necessary • Fertile women must use effective contraception and continue use for at least 6 months after last dose of golimumab • No nursing for at least 6 months after last dose of golimumab
Anakinra	B	- Insufficient data in humans	- Insufficient data in humans	- Not recommended during pregnancy and nursing - Fertile women must use effective contraception
RTX	C	- Low to undetectable lymphocyte B levels (CD19+) in newborns of mothers with RTX	- Insufficient data in humans	- Not recommended in pregnancy unless benefit outweighs risk -Effective contraception must be employed during and up to 12 months after RTX treatment -No nursing during and up to 12 months after RTX treatment
ABT	C	- Insufficient data in humans	- Insufficient data in humans	- Not recommended during pregnancy unless strictly necessary - Fertile women must use effective contraception during and up to 14 weeks after ABT treatment - No nursing while undergoing ABT treatment and up to 12 months after last dose of ABT
TCZ	C	- Insufficient data in humans	- Insufficient data in humans	- Not recommended in pregnancy unless strictly necessary - Fertile women must use effective contraception during and up to 3 months after last dose of TCZ -Risk/benefit of nursing must be evaluated individually while undergoing treatment with TCZ

ABT: abatacept; ADA: adalimumab; ETN: etanercept; IFX: infliximab; RTX: rituximab; TCZ: tocilizumab; VACTERL: vertebral defects, anal atresia, cardiac anomalies, tracheoesophageal fistula with esophageal atresia, renal abnormalities and upper limb defects.

\* FDA (U.S. Federal Drug Administration) classification on drug teratogenicity: *Category A*: adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). *Category B*: animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. *Category C*: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. *Category D*: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. *Category X*: studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

activity. In any case, the physician should study their origin and decide the course of action based on a benefit/risk ratio.

In case of lupus-like syndrome or other autoimmune disorders occurring, relevant biological therapy treatment should be discontinued (LE 2b, DR B, DA 96%).

Although rare, the possible occurrence of these phenomena should be monitored.<sup>86–88</sup> The presence of typical lupus antibodies in the absence of other signs or symptoms, is grounds for suspension.

TNF antagonist agents and TCZ should be discontinued, in a case compatible with demyelinating optic neuritis (LE 2b, DR B, DA 96%).

Treatment with TNF antagonists and TCZ has been associated with the appearance of optic neuritis, multiple sclerosis and other demyelinating disorders,<sup>49,50</sup> so drugs must be suspended in the event of occurrence.

In case of activation or the appearance of hepatitis B, C or HIV, antiviral treatment should be associated with biologic therapy (LE 4, DR C, DA 87%).

In the largest series to date, 14 patients with chronic HBV infection, 19 patients vaccinated for HBV and 19 patients with resolved HBV infection received oral antiviral therapy in combination with TNF antagonists. During treatment, levels of HBV surface antibodies disappeared or were reduced. No safety issues were found.<sup>89</sup> However, the option of temporarily suspending biological therapy until the establishment of an effective control of virus replication should not be excluded.

In the case of psoriatic lesions in patients with biologic therapy, an appropriate treatment for the lesions should be established and its suspension assessed in case this fails or if skin involvement is severe (LE 4, DR C, DA 96%).

There have been reports of cutaneous psoriasis, mainly on the palms of the hands and soles of the feet, as well as exacerbation or change in morphology of the pre-existing psoriatic lesions using these drugs,<sup>90–93</sup> which calls for vigilance against their possible occurrence.

#### Risk Management in Special Situations

If pregnancy occurs during treatment with biologic therapy, it should be discontinued (LE 4, DR C, DA 78%).

If pregnancy occurs, discontinue treatment with the biological agent.<sup>69,70,94</sup> For more information see Table 4. In men, in principle, although the possibility of association with astenoazoospermia and decreased spermatozoid mobility has been suggested,<sup>95–98</sup> there is no conclusive evidence of declining fertility in men using TNF antagonists.

In patients with biologic therapy undergoing major elective surgery it is advisable to temporarily suspend treatment (LE 4, DR C, DA 96%).

Although there is no conclusive evidence,<sup>99–103</sup> the panel recommends temporarily suspending biological therapy when the patient is to undergo major elective surgery. Although there is no universal agreement on the length of time around the surgery the drug should be discontinued, the physician should take into consideration the different half-life (or duration of immunosuppressive effect) of the agent employed, in order to decide the specific period of interruption. After surgery, the panel believes that if there are no complications or contraindications, treatment may be restored within 10–14 days.

#### Immigrants

On the other hand, biological therapy may favor, in patients from endemic areas, activation and/or spread of certain infections, unusual in our environment.<sup>104</sup> Before the start of treatment, pres-

ence of skin, digestive or respiratory symptoms in these patients, as well as hematuria, or eosinophilia, must lead the physician to rule out the coexistence of infection, mainly parasites.<sup>105</sup> In the absence of symptoms and presence of epidemiological risk factors, the physician must perform a search for fecal parasites, which if positive, must be eradicated.

Special interest has been raised by the case of *Strongyloides stercoralis* (*S. stercoralis*), a worm with a tropical distribution, mainly subtropical areas of South America and the Mediterranean, including Spain, which is able to remain in the host for years and cause serious infestation and dissemination in immunocompromised patients.<sup>106–108</sup> In patients at risk, larvae should be detected through stool testing. It is recommended that prophylactic treatment with ivermectin 200 mg/kg/day on two consecutive days be given to patients who have lived in *S. stercoralis* endemic areas at any point in their lives for more than three months, even when the stool search may be negative. Some authors recommend repeating the same pattern after 15 days and others only in the event that larvae have been initially detected, then checking for the disappearance of larvae from the stool. In the Spanish patients living in the Mediterranean basin, working barefoot in contact with wet soil is considered a risk factor.<sup>109</sup> Albendazole can be used as an alternative at 400 mg/12 h for 7 days.

In addition, in these patients it is always necessary to assess the diagnosis of infestation and dissemination in case of systemic complications and sepsis, giving treatment with empiric intravenous ivermectin.<sup>108</sup>

Finally, all those wishing to travel to areas that may be endemic or where the incidence of infection is high and those are undergoing treatment with biologic drugs should be urged to contact the relevant health authorities for information.

#### Conclusions

The SER has made various recommendations in prior consensus on the efficacy and safety of the use of biological therapies in RA, SA and PsA. Due to the emergence of new biological drugs and the large volume of information currently available, it has decided to make a specific and separate set of recommendations on managing the risk of using biological therapy regardless of the underlying disease.

In addition, there is no doubt that the availability of explicit recommendations covering all aspects of safety related to these treatments is essential to a good clinical practice as has been shown in this document.

We must insist that the prescription drug outside the indications and recommendations used for marketing authorization affects the physician's professional responsibility.

#### Financing

This study was financed in part by the subprogram RETICS, RD08/0075 (RIER) of the Instituto de Salud Carlos III (ISCIII), within the VI PN de I + D + i 2008–2011 (FEDER).

#### Conflict of Interest

Dr. Collantes has received research grants (5000 €/person year or more) from MSD, and speakers fees (5000 €/year or more) from Abbott. Dr. Mulero, research grants (5000 €/person year or more) from MSD and Pfizer, Abbott. Dr. García de Vicuña, research grants (5000 €/person year or more) from MSD, Abbott, BMS, Roche. Dr. Cañete, research grants (5000 €/person year or more) from Abbott. Drs. Batlle, Loza, Sanz, Linares, have no disclosures to make.

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