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Update of the Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in rheumatoid arthritis

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ABSTRACT

Objective: To provide a reference to rheumatologists and to those involved in the treatment of RA who are using, or about to use biologic therapy.
Methods: Recommendations were developed following a nominal group methodology and based on systematic reviews. The level of evidence and grade 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 Delphi technique.
Results: We have produced recommendations on the use of the seven biologic agents available for RA in our country. The objective of treatment is to achieve the remission of the disease as quickly as possible. Indications and nuances regarding the use of biologic therapy were reviewed as well as the evaluation that should be performed prior to administration and the follow up of patients undergoing this therapy.
Conclusions: We present an update on the SER recommendations for the use of biologic therapy in patients with RA.

Actualización del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la artritis reumatoide

Palabras clave:
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RESUMEN

Objetivo: Servir de referencia para reumatólogos e implicados en el tratamiento de la artritis reumatoide que vayan a utilizar o consideren la utilización de terapias biológicas en su manejo.
Métodos: Las recomendaciones se emitieron siguiendo la metodología de grupos nominales y basadas en revisiones sistemáticas. 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.
Resultados: Se realizan recomendaciones sobre el uso de los siete agentes biológicos disponibles para la artritis reumatoide en la actualidad en nuestro país. El objetivo del tratamiento es lograr la remisión de

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la enfermedad lo más precozmente posible. Se revisan las indicaciones y matizaciones del uso de terapias biológicas y cuál debe ser la evaluación previa y la vigilancia del paciente con estos fármacos.
Conclusiones: Se presentan las actualizaciones a las recomendaciones SER para el uso de terapias biológicas en pacientes con artritis reumatoide.

Introduction

Rheumatoid Arthritis (RA) is a disease characterized by chronic inflammation of the joints, affecting 0.5% of the adult population in Spain.[1] In most of the cases, its course is progressive and leads to irreversible joint damage, which in turn causes patient disability, a reduction in the quality of life and premature mortality. However, the past few years have shown advances of great impact in the treatment of the disease, which contributes to the modification of this somber analysis.

The treatment of RA is directed toward controlling inflammatory activity, avoiding progression of the joint structural lesion and preventing patient disability. Although non-steroidal anti-inflammatory drugs provide symptomatic relief, their efficacy is marginal at best and treatment is based on the use of the so-called disease-modifying anti-rheumatic drugs (DMARD). These are the only agents proven, though controlled trials, to act against the different manifestations of RA. There are two groups of drugs that reunite these characteristics: traditional DMARD and biologic therapy. The first are a group of small synthetic molecules, with an occasionally poorly defined mechanism of action or with a therapeutic target that is not precisely that which is involved in the pathogenic immune response process. In this document, the term DMARD specifically refers to this type of medication.

Biological therapies are, according to the European Drug Agency (EDA), products used for the treatment of diseases elaborated from cultured cells in cell banks. With the exception of microbial metabolites such as, for example, antibiotics, carbohydrates and other low molecular weight compounds. These therapies have been designed in a manner that acts specifically against a therapeutic target considered as important for a disease pathogenic process.

One of the greater advances produced in the past years regarding RA is the modification of the therapeutic strategy. The two key elements in this change are the early use of DMARD and establishing a concrete therapeutic objective, such as achieving remission or a low degree of disease activity.[2-4] This has been proven to have as much importance as the drugs employed in order to achieve it.[5]

The application of these new strategies, along with the availability of an ever-greater number of biologic agents, has sensibly improved our capacity to induce remission in many patients with RA and to significantly modify its progression in others. However, it must be taken into account that even the new biologic agents do not achieve a necessary response in 40%-50% of patients, and they tend to lose efficacy with time.[6] This makes it essential to have them all in a therapeutic arsenal for this disease.

The high cost of these drugs and the still scarce information on their long-term safety forces their rational use. Therefore it is advisable to integrate their use within an integral therapeutic strategy for the disease.

The present Consensus Document of the Spanish Society of Rheumatology (SER) is an update on the last document published in 2006. Its recommendations are centered on the treatment of RA with biologic agents in adults. The intention of these recommendations is not to serve as a treatment protocol but to improve assistance care and help in therapeutic decision making processes. This document should also serve as reference both to rheumatologists as well as all those, be it from some other position, involved in the treatment of RA.

Methods

To carry out this consensus, we used a modification of the RAND/UCLA[7] methodology. Nominal groups were created and Delphi surveys were carried out, as well as systematic reviews of controversial recommendations.

A panel of experts on RA was created based on the following criteria: 1) that they had published articles on RA, and 2) that the articles were published in MEDLINE, Reumatología Clínica or *Revista Española de Reumatología*. The members of the panel received a dossier with the previous consensus, GUIPCAR and all of the new clinical trials published from January 2006 until November 2008 with the GUIPCAR search strategy for clinical RA trials.

Two meetings of the nominal group were carried out and moderated by members of the research unit of the Spanish Society of Rheumatology. In the first meeting, proposals of modification of the 2006[8] updated document were elaborated and discussed, and a Delphi survey based on this modifications was applied. With the results of the Delphi survey, the most controversial recommendations, and those of greater interest for the consensus were decided upon. From this point, members of the panel carried out questions that could be answered through a systematic review. In the second meeting, results of the systematic review were presented, all of the modifications were discussed again and consensus recommendations were generated. Lastly, the degree of agreement of the recommendations was evaluated and the definite document was written.

The degree of agreement was defined as the percentage of consensus between panelists obtained by voting on each recommendation through an anonymous survey. The degree of evidence and recommendation were classified according to the Center for Evidence Based Medicine de Oxford model.[9]

Prior considerations

Doses and guidelines recommended for the most relevant DMARD

Although all of the DMARD have shown to be effective to a greater or lesser degree in controlled studies, the panel considers, as the most relevant DMARD, taking into account their speed of action, clinical efficacy, influence on the progression of radiological lesions and tolerance, methotrexato (MTX) and leflunomide (see GUIPCAR[10]). Doses and guidelines for the use of these two drugs as recommended by the panel appear summarized in Table 1, along with the main contraindications and adverse events.

This opinion does not exclude the use of other DMARD such as sulphasalazine, antimalarials (cloroquine and hydroxicloroquine), cyclosporine, aurothyomalate sodium or azathioprine, but their use is not to be considered as necessary before installing biologic therapy.

Table 1
Main disease modifying anti-rheumatic drugs (DMARD) according to the drug insert unless otherwise specified

Active ingredient	Dose and form of administration	Indications	Contraindications	Adverse events*
Leflunomide	– Dose: 10-20 mg – Via: orally – Frequent: daily. Start with 100 mg/day for 3 days, or start directly without loading dose	– Active RA	– Allergy to active ingredient or vehicle – Liver failure, severe infection, severe immunodeficiency, important cytopenia, moderate/severe renal failure, severe hypoproteinemia – Pregnancy and lactation	– Very frequent: not mentioned in insert – Frequent: leukocytopenia, nausea, diarrhea, oral ulcers, tenosynovitis, ↑ transaminases, ↑ creatinphosphokynase, headache – Infrequent: rash, anxiety, anemia – Rare: pancytopenia, interstitial lung disease, hepatitis, severe hypertension, pancreatitis
Methotrexate	– Dose: 7.5-25 mg – Via: orally or parenteral – Frequency: weekly. Start at 7.5-10 mg/week for 4 weeks and ↑ 2.5-5 mg every 2-6 weeks – Administer folic acid 5-10 mg/week – Adjust dose if renal failure present – If oral route is ineffective, parenteral dose might be considered	– Active RA	– Allergy to the active ingredient or vehicle – Chronic liver disease, alcoholism, liver failure, severe renal failure, blood abnormalities, immunodeficiency – Pregnancy and lactation	– Very frequent: stomatitis, nausea, ↑ transaminases – Frequent: oral ulcers, headache, anemia, leucocytopenia, thrombocytopenia, pneumonitis – Infrequent: lymphoma, ↑ rheumatic nodules, cirrhosis, liver fibrosis – Rare: sepsis, neoplasia, renal failure, lung fibrosis

RA: rheumatoid arthritis.
Data obtained from Vademecum, GUIPCAR, EMEA, MSC and Cochrane library.
* Adverse events: very frequent (at least once every 10 patients); frequent (once every 100 patients); infrequent (at least once every 1,000 and less than once every 100); rare (at least once every 10,000 and less than once every 1,000 patients).

Doses and guidelines recommended for these drugs can be consulted in GUIPCAR.[11]

Available agents in biologic therapy

We currently have seven biological agents available for the treatment of RA: three against tumor necrosis factor (anti-TNF)—a fusion protein with the soluble receptor etanercept (ETN) and two monoclonal antibodies, infliximab (IFX) and adalimumab (ADA)—, an interleukin inhibitor (IL) 1—anakinra—, a monoclonal antibody against B lymphocytes—rituximab (RTX)—, a modulating fusion protein for T cell activation—abatacept (ABA)—, and a monoclonal antibody vs. the IL-6 receptor—tocilizumab (TCZ). Table 2 summarizes the main characteristics of these agents. The three anti-TNFs, anakinra and TCZ are approved in Spain as a first line biologic in patients with DMARD failure, while RTX and ABA are approved for patients after failing to anti-TNF.

In controlled studies of RA patients and an insufficient response to DMARD, mainly MTX, the three anti-TNFs, especially when combined with MTX, are superior to this drug employed as monotherapy, both from the clinical activity and radiological progression standpoint.[12-14] In addition, controlled studies in patients with early RA have shown that its treatment with any anti-TNF, especially if combined with MTX, is capable of inducing remission in a sizable proportion of patients, as well as avoiding the development of radiological lesions or stopping its progression to a greater degree than MTX alone.[15-17] There is no data that confirms the superiority of one anti-TNF over another, making the concrete decision on which one to use dependent on the physician's criteria and each patients particular circumstances. However, attention must be called upon their particular structure, antigenicity and mechanism of action, making the lack of response to one not necessarily a factor in the response to any other. In this sense, there is data that suggests that patients that have not responded to an anti-TNF may satisfactorily respond to another.[18] Therefore, the panel considers that the three anti-TNFs are necessary and not interchangeable. Although ADA and ETN can be employed as monotherapy, controlled, double blind studies with these two drugs indicate that they are more effective when administered along with MTX at an adequate dose (15-20 mg weekly).[15,17,19] Therefore, when administering anti -TNF, combination with MTX is currently the most appropriate way, unless the patient has presented toxicity or intolerance related to the latter drug. There are no controlled studies that demonstrate that the combination with a DMARD different from MTX and anti-TNF improves their efficacy. However, it is frequent practice that, in patients with intolerance to MTX, anti-TNF is combined with a different DMARD, especially leflunomide.[20] Curiously, in a controlled study, combined treatment with sulphasalizine and ETN was not more effective than monotherapy with ETN after 6 months,[21] but after 2 years there were differences in favor of the combination, at least regarding the DAS.[22]

Another available agent, anakinra, the human recombinant form of the IL-1 receptor antagonist, has shown efficacy vs. placebo, both in symptom improvement of RA as for radiological progression.[23] Although it has never been compared in controlled studies with other biologics, there is a generalized perception that their efficacy is inferior to that of anti-TNFs. On the other hand, it is interesting to point out that Still's disease, both in children and adults, in which sometimes response to DMARD or anti-TNF is unsatisfactory, uncontrolled observations indicate good, or even excellent response with anakinra.[24,25]

RTX is a chimerical monoclonal antibody directed specifically against CD20, a molecule that is expressed selectively on the surface of B cells; this drug produces selective and prolonged depletion of this type of lymphocyte. This agent has shown efficacy both in patients that have failed to respond to DMARD[26] (although it has not been approved as a first line biologic agent) as in patients with an insufficient response to anti-TNF.[27] In this sense, RTX is currently the only biologic with a demonstrated impact on structural damage in patients with an incomplete response to anti-TNF.[28] It has recently been shown that in early RA patients, RTX in combination with MTX is superior to MTX as monotherapy.[29] However, such an indication is not approved in Europe.

ABA is a fusion protein constituted by the CTLA4 receptor fused with a human IgG, inhibiting the binding of B7 with CD80 and therefore interfering with the so called second signal necessary for T cell activation. In controlled studies with this agent it has shown, in patients with an incomplete response to MTX, that the combination with ABA is superior from a clinical and radiological standpoint to

Table 2
Commercialized biologic agents. Summary of drug insert

Active ingredient	Dose and administration	Indications	Contraindications	Adverse events*	Commercial name
Abatacept	– Dose (according to body weight): < 60 kg: 500 mg 60-100 kg: 750 mg > 100 kg: 1,000 mg – Via: iv perfusion for 30 min – Frequency: after first dose, other at 2 and 4 weeks. Then one every 4 weeks	– Moderate to severe RA after inadequate response or intolerance to DMARD among them at least one anti-TNFα – Not recommended to be associated with anti-TNFα – Not enough evidence to recommend concomitant infection with anakinra, rituximab or tocilizumab	– Allergy to the main ingredient or vehicle – Severe and uncontrolled infections	– Very frequent: headache – Frequent: nausea, herpes, respiratory/urinary infection – Less frequent: skin cancer, cytopenia, psoriasis – Rare: septicemia	ORENCIA®, vial 250 mg
Adalimumab	– Dose: 40 mg – Via: subcutaneous – Frequency: every 2 weeks. Can be administered once a week if there is no response to standard dose	– Active moderate or severe RA in combination with MTX (except when contraindicated) after an inadequate response or intolerance to other DMARD, including MTX – Severe, progressive active RA with no prior MTX use – Association with etanercept, anakinra or abatacept not recommended – Not enough evidence to recommend joint administration with rituximab, tocilizumab	– Allergy to the active ingredient or vehicle – Active TB, severe infection – Moderate to severe heart failure (NYHA class III/IV)	– Very frequent: injection site reaction (pain, erythema) – Frequent: headache, respiratory/urinary infection, herpes, diarrhea – Infrequent: SLE, arrhythmia, TB, sepsis, cytopenia – Rare: heart failure, multiple sclerosis, lymphoma, and solid malignant tumor	HUMIRA®, syringe/pen 40 mg
Anakinra	– Dose: 100 mg – Via: subcutaneous – Frequency: daily. Attempt to administer at the same hour	– RA in combination with MTX in patients who have not responded to MTX alone	– Allergy to the main ingredient, vehicle or proteins from *E. Coli* – Severe renal failure (Crcl < 30 ml/min)	– Very frequent: injection site reaction, headache – Frequent: neutropenia, severe infection	KINERET®, 100 mg syringe
Etanercept	– Dose: 25 or 50 mg – Route: subcutaneous – Frequency: 25 mg two times per week (range 72-96 h), 50 mg once a week	– Moderate to severe active RA combined with MTX (unless contraindicated) after an inadequate response or intolerance of other DMARDs including MTX – AR severe, active, progressive no previous use of MTX – Not recommended to associate with anakinra or abatacept – There is insufficient evidence to recommend administration of rituximab, tocilizumab	– Allergy to active ingredient or excipients – Sepsis or risk of sepsis – Active infections	– Very common reaction site injection, respiratory infection, urinary, skin – Frequent: allergy, autoantibodies – Uncommon: severe infections, thrombocytopenia, psoriasis – Rare: pancytopenia, TBC, LES	ENBREL®, syringe 25 and 50 mg

Infliximab	– Dose (by weight): 3 mg/kg – Route: IV infusion for 2 hours – Frequency: after first dose, another at 2 and 6 weeks. After one every 8 weeks. The dose may be increased to 7.5 mg/kg/8 weeks or may shorten the interval to 4-6 weeks if there is inefficiency or recurrence	– Moderate to severe active RA in combination with methotrexate (unless contraindicated) after an inadequate response or intolerance to other DMARDs including MTX – AR severe, active, progressive no previous use of MTX or other DMARDs – Not recommended etanercept or anakinra associate – There is insufficient evidence to recommend administration of rituximab, abatacept, tocilizumab	– Allergy to active substance, Excipients or other murine proteins – Active TB, severe infections – Moderate to severe heart failure (NYHA class III/IV)	– Very common: infusional reaction – Frequent: headache, respiratory infection, herpes, diarrhea – Uncommon: SLE, tuberculosis, sepsis, cytopenia – Rare: ICC, multiple sclerosis, lymphoma	REMICADE®, 100 mg vial
Rituximab	– Dose: 1,000 mg – Route: IV infusion. It is recommended to administer 100 mg iv methylprednisolone (or equivalent) 30 min before – Frequency: another infusion at 2 weeks. Cycle can be repeated at 6-12 months	– Severe active RA in combination with methotrexate (unless contraindicated) after an inadequate response or intolerance to DMARDs including one or more anti-TNF α – Not enough evidence to recommend the administration with anti-TNF α, abatacept, tocilizumab	– Allergy to active ingredient or excipients – Serious infections and active – Severe heart failure (NYHA class IV) or uncontrolled severe heart disease	– Very common: mild infusional reaction, upper respiratory infection – Frequent: urinary tract infection, high cholesterol, migraine, paresthesia – Uncommon: severe infusion reactions, serious infections – Rare: severe cardiac disease	MABTHERA®, vial 100 mg and 500 mg
Tocilizumab	– Dose (by weight): 8 mg/kg (not less than 480 mg). Dose adjustment if there is alteration of liver enzymes or low absolute neutrophil count or platelets – Route: IV infusion – Frequency: every 4 weeks	– AR active moderate to severe in combination with methotrexate (unless contraindicated) after inadequate response or intolerance to DMARDs or anti-TNF α – There is insufficient evidence to recommend administration with anti-TNF α, abatacept, rituximab	– Allergy to top active or excipients – Serious infections and active	– Very common: upper respiratory infection – Frequent: cholesterol, herpes, elevated transaminases, hypertension, neutropenia – Uncommon: hypertriglyceridemia, elevated total bilirubin	ROACTEMRA®, 20 mg vial

DMARD, disease-modifying drug; IV, intravenous; MTX, methotrexate; NYHA, New York Heart Association; RA, rheumatoid arthritis, SLE, systemic lupus erythematosus; TBC, tuberculosis; TNF, tumor necrosis factor.
The data in this table were obtained from the data sheet of the Spanish Agency of Medicines.

* Adverse events: very common (at least 1 in 10 patients), frequent (at least 1 in 100) rare (at least 1 in 1,000 and less than 1 in 100) rare (at least 1 of 10,000 and less than 1 in 1,000 patients).

monotherapy with MTX[30] (however, ABA is not approved as first line therapy in Europe). In patients with incomplete response to anti-TNF, ABA combined with MTX has been shown to be clinically superior to MTX monotherapy.[31]

TCZ, a humanized monoclonal antibody vs. the IL-6 receptor is the latest biologic agent available in Spain for the treatment of RA. A wide program of studies in phases II and III have shown the usefulness of this drug in different profiles of patients with RSA. In fact, TCZ has shown efficacy in patients unresponsive to DMARD,[32,33] as well as in patients who had not yet received MTX[34] and in those that had responded inadequately to anti-TNF.[35] TCZ is the only biologic agent that has proven superior to MTX as monotherapy.[34] This has been proven both for clinical manifestations as well as in the delay of the progression of radiological damage.[36-38]

Clinical, functional and radiological evaluation of rheumatoid arthritis

In the standardized evaluation of RA it is recommended that the following measures be used (evidence level [EL] 1b; degree of recommendation [DR] A; degree of agreement [GA] 86.1%):
Activity:

- Number of painful (NPJ) and swollen joints (NSJ).
- Global disease assessment by the patient and the physician (scale of 0 to 100).
- Acute phase reactants (ESR, CRP).

Structural damage: any radiological evaluation that includes the hands and feet, yearly for the first 3-4 years of the disease or when starting treatment with biologic agents.

Function: HAQ[39] or other questionnaires, at least once a year.

The systematic gathering of recommended variables allows for the calculation of the different indexes that have been validated to perform an objective estimate of disease activity: DAS, DAS28, SDAI, CDAI.[40-44] The first two are based on four of the six previously mentioned variables: NPJ and NSJ (on 66/68 or 28 joints respectively), ESR and the global assessment of disease as performed by the patient. SDAI uses all of the variables with CRP as an acute phase reactant (not included in CDAI), but does not ponder each variable.

Although the panel recommends the periodic evaluation of radiological progression in hands and feet, it is evident that, depending on the pattern of joint affection of each patient, those x-rays that are considered as necessary should also be carried out with similar periodicity.

Each therapeutic decision should be preceded by an objective evaluation of disease activity, preferably using DAS28 and/or SDAI or, in its absence, by documenting one of the components of those indexes. The evaluation has to be performed at least every three months if the therapeutic objective has not been reached and at least every 6 months once it has been achieved (EL, 5; DR, D; DA, 84.6%).

Although any of the validated indices can be used to monitor the activity of RA, experts consider that the joint counts necessary to calculate the classic DAS are to extensive to be carried out in daily clinical practice. On the other hand, having a cutpoint for DAS28 and SDAI allows for a more objective vision than that of an isolated evaluation of its components. Therefore it is considered that DAS28 and SDAI are the ideal indices to evaluate the therapeutic objective, although the use of other validated indices is not discouraged.

Therapeutic objective in rheumatoid arthritis

The panel considers that currently the idea of curing RA is a utopia and the objective of treatment should be achieving disease remission. Although this concept is well known to rheumatologists, the objective description of this state of remission is controversial. Most of the proposed definitions of remission are based on clinical parameters, but in the past few years ecography and magnetic resonance have manifested that patients who clinically could be classified as in remission presented synovitis evident with these imaging techniques. However, due to the small amount of evidence that reflects the impact of these findings and the lack of standardization and generalization of these resources, the panel opted for a clinical definition of remission.

Remission is defined as reaching any of the limits established for each one of the compared disease activity indexes such as DAS28<2.6 or SDAI<5 (LE, 1b; DR, A; DA, 83.1%).

The fact that the cutpoint employed in order to define remission through DAS28 is a mere mathematical transformation of the estimate of the original DAS is an inconvenience that must be taken into account. This has led other authors to propose different remission cutpoints for the DAS28 than those suggested by Nijmegen,[45] which waver between 3.5 and 2.4.[46,47] In the case of SDAI, different cutpoints have also been suggested, oscillating between 3.3 and 5.[43,44]

The therapeutic objective is to achieve remission of the disease, or instead, a low degree of disease activity, quantitatively defined through contrasting the cutpoints of activity, such as DAS28<3.2 or SDAI<11. The therapeutic objective is not considered as reached if, in spite of a low degree of activity there is persistent inflammation, unresolved with local therapeutic measures, in important joints for the patient or significant progression of radiological lesions (LE, 1b; DR, A; DA, 93.1%).

Some practical considerations must be taken into account when applying disease activity indexes to individual patients: 1) women and patients with longer time since onset of disease have greater values of DAS 28 due to greater ESR[46,48-50]; 2) other variables such as TJC[51,52] or the global evaluation of disease can also bias the result of DAS28and SDAI, particularly the former, where painful joints are weighed much higher than swollen ones, and *3)* in the case of SDAI, CRP values are not normalized and in some cases can lead to excessively high SDAI scores.

Therefore, the panel considers that, in patients who have reached these generic improvement parameters but persist with inflammation in some important joint, or significant progression is detected on x-rays, the therapeutic objective would not have been reached and a change in treatment would be indicated.

Considerations on the initial treatment of rheumatoid arthritis

There is evidence that intensive and early treatment of RA improves its progression, making it necessary to start DMARD treatment as soon as possible (LE, 2b; DR, B; DA, 96.2%).

Evidence suggests that early and energetic therapy lead to better results.[2,3,53,54] In fact, the response and evolution of disease after treatment, started at 3 months, is much higher than that obtained when this is delayed to 12 months.[3] Therefore, the need for installing DMARD treatment as soon as the diagnosis of RA has been reached is well established. The greatest objection to early DMARD treatment is the possibility of treating a patient with transient polyarthritis as RA; but in any case, polyarthritis lasting more than 12 or 14 weeks has a high probability of persisting. Therefore, even when the American College of Rheumatology (ACR) criteria for RA are not met, faced with a high probability of being faced with early onset RA, the panel considers that treatment with DMARD should be started in these patients.

Treatment of RA (NSAID and/or steroids and DMARD) in its initial phase needs frequent adjustment, making it necessary to monitor the patient frequently. The objective is to: 1) reach the therapeutic

objective as soon as possible, and 2) rapidly identifies cases resistant to initial treatment.

Initial treatment must include one of the relevant DMARD, of which MTX is a good example. MTX has to be administered in rapid increments until a dose of 15-20 or even 25 mg a week is reached in 8 weeks if there is no good clinical response. There is evidence that strict monitoring in the initial phase of RA is capable of inducing remission in an elevated percentage of patients[4,5]; all of this leads to less disability in the medium and long terms and, therefore, to a reduction in the severe consequences of this process.

In patients with an insufficient response or intolerance to MTX, leflunomide is an alternative. The use of sulphasalazine in Spain has traditionally been low.[55] It is very likely that this is due in part to the fact that the Spanish formulation lacks enteric protection and is poorly tolerated

Establishing RA clinics is recommended (LE, 5; DR, D; DA, 83.1%).

In order to optimize therapeutic results, the panel considers especially important that patients with RA have the possibility of quick access to specialized treatment (early RA units). Response to treatment must be evaluated rigorously and periodically, with standardized procedures.

Indications of biologic therapy

The choice of biologic is an obligation of the patients' attending physician. The biologic to be administered must be chose in function of: 1) the indication according to the insert; 2) the clinical situation and general conditions of the patient, and 3) the clinical experience of the prescribing physician. The decision should never be made with economic reasons in mind or by persons that lack clinical experience or direct responsibility in the treatment of the patient.

Treatment after DMARD failure

Patients who have received treatment with at least one relevant DMARD and have not reached the therapeutic objective must be considered candidates for biologic therapy (LE, 1b; DR, A; DA, 95.3%).

Before employing biologic therapy, a patient with RA must have received treatment with at least one DMARD, preferably MTX or LFN, in monotherapy or in combination and at an adequate dose. Only in exceptional cases should biologic therapy be considered as initial treatment (LE, 1b; DR, A; DA, 95.3%).

Drugs that, according to their insert, are indicated as first line therapy are the three anti-TNF (ADA, ETN and IFX) and TCZ, but evidence is insufficient to recommend specific therapy.

In the particular case of patients in which RA has entered remission with a specific DMARD and then presented reactivation after suspending the drug, a new DMARD treatment cycle with the drug that induced remission should be considered before considering biologic therapy.

Determined comorbidities, such as chronic liver disease, infection with hepatitis C virus, can lead to the consideration of biologics before trying treatment with DMARD.

Biologic therapy from the onset

Given the evidence available that TNFα or IL-6 inhibitors induce rapid suppression of inflammation and have greater efficacy than DMARD in avoiding structural damage, the panel considers that evaluating the possibility of starting treatment with an anti-TNF (IFX, ETN, ADA) or TCZ, in combination with MTX or as monotherapy in case the first is counter-indicated, in patients with RA of at least one year since onset and who present an especially severe progression, is justified.[15,16,19,56-59]

Evaluating response and modifications to treatment in patients with anti-TNF

Therapeutic response to the first biologic must be evaluated at 3-4 months of starting treatment. If the objective has been reached, periodic examinations must be carried out every 3-6 months. If the objective has not been reached or the patient stops responding, the panel recommends making a new therapeutic decision (LE, 1b; DR, A; DA, 90.7%).

In this sense, only three biologic agents from those currently available have shown their efficacy after failing to respond to anti-TNF: ABA, RTX and TCZ,[27,28,31,35,60-62] through randomized, double blind, placebo controlled trials. Recently, data with another anti-TNF (golimumab), not yet commercialized, has been published, which also shows an efficacy similar to the abovementioned agents.[63] However, the global experience that is being collected with biologic agents and the results of other studies confirm that any therapeutic alternative used in patients with failure to a previous biologic may result effective.

Among the alternatives to biologics we can find:

1. If the anti-TNF is being employed as monotherapy, the possibility of adding MTX, with a rapid dose increase to the treatment must be evaluated before switching to another biologic.
2. If the anti-TNF is being used in combination with MTX and therapeutic response is not achieved, the following options might be considered, in no particular order of preference (DA 87.6%):

- If the patient is being treated with IFX, the dose may be increased or the administration interval may be shortened (LE, 4; DR, C).[64] After the editorial review of this document, a clinical trial was published (LE, 2b) which did not back the dose increase of IFX from 3 to 5 mg/kg in patients who had not responded to the commonly used doses.[65] It is only one, well-performed study that uses a maximum dose below those approved. No other evidence suggesting shortening dose intervals has appeared.
- Switch to another anti-TNF, independently of it being a monoclonal antibody or a soluble receptor. Numerous observational studies have repeatedly shown that achieving a significant clinical response with a third anti-TNF is highly unlikely (LE, 2b; DR, B).[66,67]
- Change the therapeutic target (RTX, ABA, TCZ) (LE, 2b; DR, B).[27,35,60,62,68]
- If the patient was in treatment with TCZ as a first line agent, no information is available in order to emit a specific recommendation, although cumulative experience with biologics does not suggest that a different pattern than that seen with other anti-TNF will be observed (LE, 5; DR, D).

  The simultaneous administration of biologics mentioned in this document is contra-indicated (LE, 5; DR, D; DA, 88.5%).

  Combination of biologics in RA has shown an increase in the risk for infection without a clear clinical advantage, making their combination currently contra-indicated.

The following are acceptable options in patients who have achieved remission (LE, 5; DR, D; DA, 89.2%):

- Maintain treatment with biologics.
- Attempt to reduce the dose, prolong the administration interval or even suspend the biologic agent.

Any modification to therapy in a patient in remission requires that this clinical situation is maintained, although the timeline is yet to be defined. Reducing or suspending steroids before modifying the dose of biologics is recommended. Reducing the dose of the concomitant

Table 3
Actions and monitoring of biological therapies in patients with rheumatoid arthritis

Active	Before treatment	During treatment	Discontinuation of treatment
Anti-TNFα: adalimumab, etanercept, infliximab	1) Clinical aspects: – Discard: active infection (including TB), cancer, heart failure, cytopenia, demyelinating disease, significant comorbidity – Discard recent contact with TB patients – Discourage pregnancy 2) Investigations: – CBC – Bookmarks HBV, HCV serology – Chest radiograph – Mantoux and booster 3) Other actions: – Pneumococcal vaccine and influenza vaccination – Assess the HBV vaccine – Avoid vaccinations with live attenuated or germs	1) Clinical aspects: – Emergence of infections (including TB), severe cytopenia demyelinating optic neuritis, cancer – Onset or worsening heart failure 2) Investigations: – Complete blood count and general biochemistry (monthly during the first 3 months, then every 3-4 months) 3) Other actions: – Depending on the patient's progress	– Appearance of cancer, or demyelinating optic neuritis, severe cytopenia or other serious events related to drug – Temporary suspension if infection or major elective surgery in perioperative period – Assess whether pregnant or breastfeeding
Anakinra	1) Clinical aspects: – Discard: active infection (including TB), cancer, heart failure, cytopenia, demyelinating disease, significant comorbidity – Discard recent contact with TB patients – Discourage pregnancy 2) Investigations: – CBC – Serology HBV, HCV – Chest radiograph – Mantoux and booster 3) Other actions: – Pneumococcal vaccine and influenza vaccination – Assess the HBV vaccine – Avoid vaccinations with live attenuated or germs	1) Clinical aspects: – Emergence of infections (including tuberculosis), heart failure, severe cytopenia, demyelinating optic neuritis, cancer 2) Investigations: – Blood count and general biochemistry (monthly during the first 3 months, then every 3-4 months) 3) Other actions: – Depending on the patient's progress	– Appearance of cancer, or demyelinating optic neuritis, severe cytopenia or other serious events related to drug – Temporary suspension if infection or major surgery elective in perioperative period – Assess whether pregnant or breastfeeding
Abatacept	1) Clinical aspects: – Discard: active infection (including TB), cancer, heart failure, cytopenia, demyelinating disease, significant comorbidity – Discard recent contact with TB patients – Discourage pregnancy	1) Clinical aspects: – Emergence of infections (including tuberculosis), heart failure, severe cytopenia, demyelinating optic neuritis, cancer – Onset or worsening of respiratory function in COPD patients after	– Appearance of cancer, or demyelinating optic neuritis, severe cytopenia or other serious events related to drug – Temporary suspension if infection or major surgery elective in perioperative period – Assess whether pregnant or breastfeeding

	2) Investigations: – CBC – Serology HBV, HCV – Chest radiograph – Mantoux and booster 3) Other actions: – Pneumococcal vaccine and influenza vaccination – Assess the HBV vaccine – Avoid vaccinations with live attenuated or germs	2) Investigations: – CBC and general biochemistry (monthly during the first 3 months, then every 3-4 months) 3) Other actions: – Depending on the patient's progress	
Rituximab	1) Clinical aspects: – Discard: active infection (including TB), cancer, heart failure, cytopenia, demyelinating disease, significant comorbidity – Discard recent contact with TB patients – Discourage pregnancy 2) Investigations: – CBC – Serology HBV, HCV – Concentration of immunoglobulins – Chest radiograph – Mantoux and booster 3) Other actions: – Pneumococcal vaccine and influenza vaccination – Assess the HBV vaccine – Avoid vaccinations with live attenuated or germs	1) Clinical aspects: – Emergence of infections (including tuberculosis), heart failure, severe cytopenia, demyelinating optic neuritis, cancer 2) Investigations: – CBC and general biochemical lipid profile (monthly during the first 3 months, then every 3-4 months) 3) Other actions: – Depending on the patient's progress	– Appearance of cancer, or demyelinating optic neuritis, severe cytopenia or other serious events related to drug – Temporary suspension if infection or major surgery elective in perioperative period – Assess whether pregnant or breastfeeding
Tocilizumab	1) Clinical aspects: – Discard: active infection (including TB), cancer, heart failure, cytopenia, demyelinating disease, significant comorbidity – Discard recent contact with TB patients – Discourage pregnancy 2) Complementary tests: – CBC – Serology HBV, HCV – Chest X-ray – Mantoux and booster 3) Other actions: – Antipneumococcal and flu vaccines – Evaluate HBV vaccine – Avoid live vaccines or attenuated	1) Clinical aspects: – Emergence of infections (including tuberculosis), heart failure, severe cytopenia, demyelinating optic neuritis, cancer 2) Investigations: – CBC and general biochemical lipid profile (monthly during the first 3 months, then every 3-4 months) 3) Other actions: – According to patient progression	– Appearance of cancer, or demyelinating optic neuritis, severe cytopenia or other serious events related to drug – Temporary suspension if infection or major surgery elective in perioperative period – Assess whether pregnant or breastfeeding

CBC indicates complete blood count; COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HCV, hepatitis C virus; TB, tuberculosis.

DMARD is not suggested before the reduction in the dose of biologic, except in cases of DMARD toxicity.

Once all treatment options with biologic agents have been explored and the therapeutic objective has not been achieved, but if both the patient and the physician observe an improvement over 20% in global disease assessment, the panel recommends that treatment with the biologic chosen for the patient should be maintained.

Prior evaluation and vigilance of the patient with biologic therapy

The fact that biologic drugs have been employed mostly in RA patients with moderate to severe disease, who by themselves have a greater risk than the general population for infections,[69] lymphomas,[70] and cardiovascular disease[71] must be taken into account.

On the other hand, the panel considers that treatment of this disease must be undertaken by physicians who have experience with the use of biologics and are accustomed to the management of chronic inflammatory diseases of an autoimmune nature and drugs such as those exposed in this document. Whenever biologic therapy is indicated for the treatment of RA, the patient must be instructed on the appearance of red-flag symptoms that must be detected as a possible sign of drug safety issues. A strict follow-up of the course of treatment, in collaboration and communication with the primary care physician must be carried out. It is recommended that the official insert for all of the agents described in this document be reviewed and applying their recommendations before proceeding to the clinical use of the drug is recommended.

Table 3 shows the evaluation that is recommended before starting treatment, as well as the vigilance that must be carried out during follow-up. Although the security profile is not exactly the same in the different options of biologic therapy, currently available information led the panel to consider that the following recommendations are applicable to all of the patients about to start biologic treatment.

When a patient is about to begin with biologic therapy for RA, the possible existence of infections, cancer, heart failure, cytopenia, demyelinating disease or any other form of relevant comorbidity or contraindication for start of treatment must be taken into account (LE, 2b; DR, B; DA, 99.2%).

A Spanish registry of adverse events related to biologic therapy (BIOBADASER) has found a greater incidence of infections in patients with Ra receiving anti-TNF[72]; similar data has been published in this regard.[17,73,74] This increase is related with certain comorbidities: diabetes mellitus, high dose steroids and the concomitant use of other immunosuppresants. Infections are normally localized to the upper and lower respiratory tract, the skin and genitourinary tract. They are usually due to *Staphylococcus aureus* and gram-negative germs. Likewise, a greater frequency of herpes zoster[75] has been described, and cases of opportunistic infections such as lysteria, disseminated aspergillosis and other uncommon infections in Spain, such as hystoplasmosis and coccydioidomycosis, have been reported although their incidence has been low.[76] With the rest of the biologic agents, a greater incidence of infections has also been reported.[32,61,77]

An active, systemic or localized infection constitutes a contraindication for the start of biological therapy (LE, 4; DR, C; DA, 94.6%).

Therefore, the use of anti-TNF agents or other biologics is not recommended in patients with a history of repeat infection or sepsis. Treatment should also not be undertaken with these drugs if there is an active, systemic or localized infection. In this sense, a history of an infected joint prosthesis forces the performance, before the start of therapy with biologics, of an adequate therapeutic strategy (surgery consisting in radical elimination of infection and, if indicated, prosthetic replacement). Very special attention must be paid to the possible development of infections during treatment. If this situation arose, an early diagnosis and treatment are fundamental, as well as the temporary suppression of biologic therapy. Faced with an increase in immigrant population and in relation to their geographical origin, it is necessary to evaluate patients for reactivations of formerly unusual infections in our country. Once the infection has been resolved, biologic therapy can be restarted.

A greater incidence of tuberculosis (TB) has been seen in patients with RA who received anti-TNF, especially with monoclonal antibodies.[78-81] In most cases, TB appeared after 3 months of treatment, indicating a reactivation of latent TB, and presenting an infrequent pattern (extrapulmonary, disseminated TB).

The panel considers an obligation to exclude TB in all patients who are about to start biologic therapy or have had recent contact with a TB patient, as well as investigating the possibility of latent TB. Therefore it has been proposed that history of TB infection or recent contacts be documented and a chest x-ray be performed in order to rule out active TB or radiographic signs suggestive of a past infection, as well as a tuberculin test (PPD), repeated after one to two weeks if < 5 mm (LE, 2b; DR, B; DA, 100%).

This test has been associated to a reduced risk of latent TB reactivation.[78,82] PPD or booster positive patients is considered if an RA patient has an induration ≥ 5 mm, after 72 h. Because it is impossible to know whether individuals who have been vaccinated with the Calmette-Guerin bacillus have a positive PPD due to the vaccion or latent TB infection, the same recommendations as those employed for non-vaccinated individuals must be followed. It is also important to instruct patients on the risks associated with the exposure to patients with active TB.

Treatment for latent TB infection should be installed before the start of biologic therapy under the following circumstances: 1) recent contact with a patient with documented TB; 2) a history of partially treated TB; 3) positive PPD or *booster*, and 4) residual lesions seen on the chest x-ray. The choice treatment for latent TB is isoniazide (5 mg/kg/day up to a maximum 300 mg daily) with vitamin B_6 supplements, for 9 months (LE, 2b; DR, B; DA, 98.4%).

In case the patient is intolerant to isoniazide, rifampin is recommended at a dose of 10 mg/kg/day (maximum, 600 mg a day) for 4 months. The effectiveness of these norms to prevent the reactivation of latent TB has been demonstrated in Spain by the important reduction seen in new cases of TB as documented by BIOBADASER.[82]

If the patient has recently received an adequate treatment for latent or active TB, it is unnecessary to perform prophylaxis or Mantoux (LE, 5; DR, D; DA, 93.8%). However, an exhaustive follow up is also recommended for these patients.

HBV and HCV serology is recommended in candidates for biologic therapy (LE, 4; DR, C; DA, 95.3%).

There have been described cases of HBV reactivation of infection in patients taking anti-TNF which have led to liver failure; many of them in patients with no prior liver anomalies.[83] With respect to HCV, it is unclear whether anti-TNF leads to deterioration of liver function or an increase in viral load, and improvement in some functional scores has even been described.[84-87] However, it is recommended that an exhaustive follow up is performed in patients with RA and active HCV infection if biologics are started. In relation to the Human Immunodeficiency Virus (HIV), there are series of cases in which biologics have also been effective, but an increase in the number of infections is also seen.[88] Therefore we suggest individualizing each case and evaluating risk/benefit.

The following vaccines are recommended for patients to be treated with biologics: anti-pneumococcal and the flu vaccine (LE, 3b; DR, B; DA, 95.3%).

HBV vaccination is also recommended in patients who are to be subjected to biologic therapy (LE, 3b; DR, B; DA, 83.8%).

In reference to vaccines, different publications have manifested a good humoral response in the case of anti-TNF for the influenza virus and pneumococcus,[89-91] but data is currently contradicting in the case of RTX.[92,93]

In any case, these vaccines are considered poorly effective if the patient is severely immunocompromised. Once biologics are started, live vaccines should be avoided.

Special attention must be paid to the development of infections during treatment. In this situation, early diagnosis and treatment, as well as temporal interruption of biologic therapy, are fundamental. Once the infection has resolved, biologic therapy can be restarted (LE, 5; DR, D; DA, 96.9%).

In RA patients receiving biologics who are to be subjected to surgery, the temporary interruption of therapy is recommended (LE, 4; DR, C; DA, 91.5%).

Although there is no conclusive evidence,[94-98] the panel recommends temporarily suspending biologic therapy when RA patients are to be subjected to major elective surgery, in order to reduce the risk of infection. In spite of the lack of universal agreement on the moment in which therapy is to be interrupted, it is convenient to keep the drug's half times in mind (or the duration of the immunosuppressive effect) to decide a concrete timeline for interruption. After surgery, the panel considers that, if there are no contraindicactions or complications, biologic therapy can be reinstituted after 10-14 days.

If the patient has a history of cancer, its biology and behavior must be evaluated and the possibility of a relapse must be discussed with the oncologist and the patient. If the patient contracts cancer while under treatment with a biologic, suspension is recommended (LE, 4; DR, C; DA, 90%).

With respect to the appearance of tumors in patients treated with anti-TNF, there is no evidence of an increased risk of solid tumors over what is expected in an RA patients and a high degree of disease activity.[76,99,100] In any case, special attention must be given to the detection of malignant neoplasms in subjects with RA receiving biologics. Among other situations, a clinical suspicion will be established when a discrepancy is detected between the joint counts and the serum concentration of acute phase reactants, the leukocyte count or the hemoglobin concentration.[101]

There is discordant data on lymphoproliferative diseases,[102,103] and while this question remains unclear, the use of anti-TNFα in patients with RA and a history of lymphoproliferative disease is not recommended.

Special care must be taken with anti-TNF in patients with moderato to severe heart failure because it may be aggravated (LE, 2b; DR, B; DA, 94.6%).

Although current data does not always agree,[104,105] patients with mild heart failure must be monitored and treatment suspended if worsening of the heart condition occurs. It is not recommended either for patients with underlying interstitial lung disease due to the risk (underdocumented) of worsening and death.[106,107]

Anti-TNF (and TCZ) should be suspended if a demyelinating process is suspected or optic neuritis develops, and their use is discouraged in persons with a clear history of these diseases (LE, 5; DR, D; DA, 96.9%).

Anti-TNF has been related to the appearance of optic neuritis, multiple sclerosis and demyelinating processes.[108,109] Faced with a case of any of these problems, treatment should be suspended and avoided if there is any history of one of these processes. Before prescribing an anti-TNF to patients in whom an increased risk of demyelinating disease has been contemplated, a careful evaluation of the risk-benefit ratio of the indication is indicated. The technical insert of TCZ recommends being on the lookout for possible demyelinating effects.

Biologic therapy for RA treatment is not recommended if the patient has severe cytopenia. If this appears during treatment, suspension is recommended and the search for other possible causes should be undertaken before attributing it to biologic drugs (LE, 4; DR, C; DA, 87.6%).

Rare cases of leucopenia, thrombocytopenia and aplastic anemia have been reported in patients treated with biologics.[110]

Pregnancy and lactation should be discouraged. In the case of pregnancy during treatment with biologics, suspending treatment with the biologic agent is recommended after a joint evaluation of risks and benefits (LE, 4; DR, C; DA, 90%).

In general, although there is not enough evidence,[111] patients with RA should be discouraged from receiving biological therapy during pregnancy or when lactating. In the case of pregnancy, biologic treatment should be suspended after evaluating with the patient the balance between risks and benefits. On the other hand, it is recommended that patients and their physicians discuss planning pregnancies in relation to the use of biologic drugs.

For a more detailed analysis on aspects regarding vigilance, monitoring and recommendations related with the suspension of treatment due to security motives of each biologic drug (used as indicated, at the moment of writing this consensus, for the treatment of RA in Spain), the panel recommends reviewing Table 3.

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References

1. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis. 2001;60:1040-5.
2. Lard LR, Visser H, Speyer I, Van der Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111:446-51.
3. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2004;43:906-14.

4. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364:263-9.
5. Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, Van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52:3381-90.
6. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007; 370:1861-74.
7. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica: RAND; 2001.
8. Rodríguez-Valverde V, Cáliz Cáliz R, Álvaro-Gracia Álvaro JM, Marenco de la Fuente JL, Mulero Mendoza J, Tornero Molina J, et al. III Actualización del Consenso de la Sociedad Española de Reumatología sobre terapia biológica en la artritis reumatoide. Rev Esp Reumatol. 2006;2:52-9.
9. Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009). 2009 [accessed 9/22/2009]. Available at: http://www.cebm.net/index.aspx?o=1025
10. Guía de práctica clínica para el manejo de la artritis reumatoide 2007 (versión HTML completa) [accessed 9/22/2009]. Available at: http://www.ser.es/practicaClinica/GUIPCAR_2007/Menu0_Principal.php
11. GUIPCAR. Principales fármacos modificadores de la enfermedad (FAME) 2007 [accessed 9/22/2009]. Available at: http://www.ser.es/practicaClinica/GUIPCAR_2007/Tablas/Tabla21.php
12. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48:35-45.
13. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999;340:253-9.
14. Lipsky PE, Van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med. 2000;343:1594-602.
15. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343:1586-93.
16. St Clair EW, Van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50:3432-43.
17. Breedveld FC, Emery P, Keystone E, Patel K, Furst DE, Kalden JR, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004;63:149-55.
18. Sanmartí R, Gómez-Puerta JA, Rodríguez-Cros JR, Albaladejo C, Muñoz-Gómez J, Cañete JD. Etanercept en pacientes con artritis reumatoide y escasa respuesta terapéutica a infliximab. Med Clin (Barc). 2004;122:321-4.
19. Van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54:1063-74.
20. Kalden JR, Antoni C, Alvaro-Gracia JM, Combe B, Emery P, Kremer JM, et al. Use of combination of leflunomide with biological agents in treatment of rheumatoid arthritis. J Rheumatol. 2005;32:1620-31.
21. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65:1357-62.
22. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009;68:1146-52.
23. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46:614-24.
24. Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum. 2005;52:1794-803.
25. Dinarello CA. Blocking IL-1 in systemic inflammation. J Exp Med. 2005;201:1355-9.
26. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54:1390-400.
27. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54:2793-806.
28. Keystone E, Emery P, Peterfy CG, Tak PP, Cohen S, Genovese MC, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis. 2009;68:216-21.
29. Takk PP, Rigby W, Rubbert A, Peterfy C, Van Vollenhoven RF, Stohl W, et al. Inhibition of joint damage and improved clinical outcomes with a combination of rituximab (RTX) and methotrexate (MTX) in patients (PTS) with early active rheumatoid arthritis (RA) who are naive to MTX: arandomised active comparator placebo-controlled trial. Ann Rheum Dis. 2009;68(Suppl 3):75.
30. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144:865-76.
31. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353:1114-23.
32. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371:987-97.
33. Genovese MC, McKay JD, Nasonov EL, Mysler EF, Da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58:2968-80.
34. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis. 2009 March 17; doi:10.1136/ard.2008.105197.
35. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67:1516-23.
36. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162-7.
37. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19:12-9.
38. Emery P, Keystone E, Tony HP, Cantagrel A, Vollenhoven RF, Sanchez A, et al. Tociluzumab (TCZ) rapidly and significantly improves outcomes in patients with rheumatoid arthritis (RA) who have inadequate response (IR) to TNF antagonists. Arthritis Rheum. 2008;58(Suppl 9):S617.
39. Esteve-Vives J, Batlle-Gualda E, Reig A, Grupo para la Adaptacion del HAQ a la Poblacion Espanola. Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. J Rheumatol. 1993;20:2116-22.
40. Van der Heijde DM, Van't Hof M, Van Riel PL, Van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol. 1993;20:579-81.
41. Van der Heijde DM, Van't Hof MA, Van Riel PL, Van Leeuwen MA, Van Rijswijk MH, Van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992;51:177-81.
42. Prevoo ML, Van't Hof MA, Kuper HH, Van Leeuwen MA, Van de Putte LB, Van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44-8.
43. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42:244-57.
44. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(Suppl 39):S100-8.
45. Prevoo ML, Van Gestel AM, Van THMA, Van Rijswijk MH, Van de Putte LB, Van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996;35:1101-5.
46. Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R, et al. Value of disease activity score 28 (das28) and das28-3 compared to american college of rheumatology-defined remission in rheumatoid arthritis. J Rheumatol. 2004;31:40-6.
47. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum. 2005;52:2625-36.
48. Castrejon I, Ortiz AM, Garcia-Vicuna R, Lopez-Bote JP, Humbria A, Carmona L, et al. Are the C-reactive protein values and erythrocyte sedimentation rate equivalent when estimating the 28-joint disease activity score in rheumatoid arthritis? Clin Exp Rheumatol. 2008;26:769-75.
49. Radovits BJ, Fransen J, Van Riel PL, Laan RF. Influence of age and gender on the 28-joint Disease Activity Score (DAS28) in rheumatoid arthritis. Ann Rheum Dis. 2008;67:1127-31.
50. Ahlmén M, Svensson B, Albertsson K, Forslind K, Hafstrom I. Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. Ann Rheum Dis. 2009;69(1):230-3.

51. Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B. Disease activity score-28 values differ considerably depending on patient's pain perception and sex. J Rheumatol. 2007;34:2382-7.
52. Unruh AM. Gender variations in clinical pain experience. Pain. 1996;65:123-67.
53. Quinn MA, Conaghan PG, Emery P. The therapeutic approach of early intervention for rheumatoid arthritis: what is the evidence? Rheumatology (Oxford). 2001;40:1211-20.
54. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. Arthritis Rheum. 2003;48:1771-4.
55. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: influence of new therapies and changes in management approach: analysis of the EMECAR cohort. Arthritis Res Ther. 2008;10:R138.
56. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, Van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26-37.
57. Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum. 2006;54:702-10.
58. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372: 375-82.
59. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006;54:2817-29.
60. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008;67:547-54.
61. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54:2807-16.
62. Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis. 2007;66:228-34.
63. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374:210-21.
64. Vollenhoven RF, Gullstrom E, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: Data from the Stockholm TNF registry. Arthritis Rheum. 2001;44(Suppl):S82.
65. Pavelka K, Jarosova K, Suchy D, Senolt L, Chroust K, Dusek L, et al. Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. Ann Rheum Dis. 2009;68:1285-9.
66. Brocq O, Plubel Y, Breuil V, Grisot C, Flory P, Mousnier A, et al. [Etanercept--infliximab switch in rheumatoid arthritis 14 out of 131 patients treated with anti TNFalpha]. Presse Med. 2002;31:1836-9.
67. Hansen KE, Hildebrand JP, Genovese MC, Cush JJ, Patel S, Cooley DA, et al. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol. 2004;31:1098-102.
68. Finckh A, Ciurea A, Brulhart L, Kyburz D, Moller B, Dehler S, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum. 2007;56:1417-23.
69. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46:2287-93.
70. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692-701.
71. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107:1303-7.
72. Carmona L, Gómez-Reino J, González R. Registro español de acontecimientos adversos de terapias biológicas en enfermedades reumáticas (BIOBADASER): informe de la situación a 14 de enero de 2005. Reumatol Clin. 2005;1:95-111.
73. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003;30:2563-71.
74. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46:1443-50.
75. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009;301:737-44.
76. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf. 2004;27:307-24.
77. Salliot C., Dougados M., Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009;68:25-32.
78. Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007;57:756-61.
79. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003;48:2122-7.
80. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098-104.
81. Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004;39:295-9.
82. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005;52:1766-72.
83. Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis. 2006;65:983-9.
84. Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum. 2004;51:800-4.
85. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol. 2005;42:315-22.
86. Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol. 2008;35:421-4.
87. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008;35:1944-9.
88. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008;67:710-2.
89. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007;34:272-9.
90. Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2004;33:283-8.
91. Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2009.
92. Gelinck LBS, Teng YKO, Rimmelzwaan GF, Van Den Bemt BJF, Kroon FP, Van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis. 2007;66:1402-3.
93. Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: The effect of rituximab on the humoral response. Ann Rheum Dis. 2008;67:937-41.
94. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004;25:331-5.
95. Corrao S, Pistone G, Arnone S, Calvo L, Scaglione R, Licata G. Safety of etanercept therapy in rheumatoid patients undergoing surgery: Preliminary report. Clin Rheumatol. 2007;26:1513-5.
96. Den Broeder AA, Creemers MC, Fransen J, De Jong E, De Rooij DJ, Wymenga A, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007;34:689-95.
97. Wendling D, Balblanc JC, Brousse A, Lohse A, Lehuede G, Garbuio P, et al. Surgery in patients receiving anti-tumour necrosis factor (alpha) treatment in rheumatoid arthritis: An observational study on 50 surgical procedures. Ann Rheum Dis. 2005;64:1378-9.
98. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Care Res. 2006;55:333-7.
99. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006;355:704-12.
100. Sibilia J, Westhovens R. Safety of T-cell co-stimulation modulation with abatacept in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007;25(Suppl 46):S46-56.
101. Abasolo L, Judez E, Descalzo MA, Gonzalez-Alvaro I, Jover JA, Carmona L. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum. 2008;37:388-97.
102. Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with

rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005;64:699-703.
103. Okada SK, Siegel JN. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. JAMA. 2006;296:2201-2.
104. Setoguchi S, Schneeweiss S, Avorn J, Katz JN, Weinblatt ME, Levin R, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J. 2008;156:336-41.
105. Curtis JR, Kramer JM, Martin C, Saag KG, Patkar N, Shatin D, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford). 2007;46:1688-93.
106. Martin L, Barr S, Green F, Fritzer M. Severe fatal cpmplications associated with infliximab therapy in rheumatoid arthritis. J Rheumatol. 2006;33:380.
107. Ostor AJ, Chilvers ER, Somerville MF, Lim AY, Lane SE, Crisp AJ, et al. Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. J Rheumatol. 2006;33:622-8.
108. Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. Optic neuritis occurring with anti-tumour necrosis factor alpha therapy. Ann Rheum Dis. 2007;66:1255-8.
109. Bensouda-Grimaldi L, Mulleman D, Valat JP, Autret-Leca E. Adalimumab-associated multiple sclerosis. J Rheumatol. 2007;34:239-40.
110. Keystone E.C. Safety of biologic therapies—an update. J Rheumatol Suppl. 2005; 74:8-12.
111. Ostensen M, Lockshin M, Doria A, Valesini G, Meroni P, Gordon C, et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. Rheumatology (Oxford). 2008;47(Suppl 3):iii28-31.