Arch Bronconeumol. 2016;52(1):36–45

ARCHIVOS DE BRONCONEUMOLOGIA

www.archbronconeumol.org

Special article

Consensus Document on Prevention and Treatment of Tuberculosis in Patients for Biological Treatment☆,☆☆

Isabel Mir Viladrich,[a,*] Esteban Daudén Tello,[b] Guillermo Solano-López,[b] Francisco Javier López Longo,[c] Carlos Taxonera Samso,[d] Paquita Sánchez Martínez,[e] Xavier Martínez Lacasa,[f] Mercedes García Gasalla,[g] Jordi Dorca Sargatal,[h] Miguel Arias-Guillén,[i] José Maria García García[j]

[a] *Servicio de Neumología, Hospital Son Llàtzer, Palma de Mallorca, Spain*
[b] *Servicio de Dermatología, Hospital Universitario de la Princesa, Madrid, Spain*
[c] *Servicio de Reumatología, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[d] *Servicio Aparato Digestivo, Hospital Clínico San Carlos e Instituto de Investigación del Hospital Clínico San Carlos (IdISSC), Madrid, Spain*
[e] *Servicio de Enfermedades Infecciosas, Hospital del Mar, Barcelona, Spain*
[f] *Unidad control de Tuberculosis, Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain*
[g] *Servicio de Medicina Interna, Unidad de Enfermedades Infecciosas, Hospital Son Llàtzer, Palma de Mallorca, Spain*
[h] *Servicio de Neumología, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain*
[i] *Servicio de Neumología, Hospital Universitario Central de Asturias-Instituto Nacional de Silicosis, Oviedo, Asturias, Spain*
[j] *Servicio de Neumología, Hospital San Agustín, Avilés, Asturias, Spain*

ARTICLE INFO

Article history:
Received 20 January 2015
Accepted 24 April 2015
Available online 23 December 2015

Keywords:
Chronic inflammatory diseases
Latent tuberculosis infection
Biologic therapies
Interferon-gamma release assays

ABSTRACT

Tuberculosis risk is increased in patients with chronic inflammatory diseases receiving any immunosuppressive treatment, notably tumor necrosis factor (TNF) antagonists therapy. Screening for the presence of latent infection with *Mycobacterium tuberculosis* and targeted preventive treatment to reduce the risk of progression to tuberculosis disease is mandatory in these patients.

This Consensus Document summarizes the current knowledge and expert opinion of biologic therapies, including TNF-blocking treatments. It provides recommendations for the use of interferon-gamma release assays (IGRA) and tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection in these patients, and for the type and duration of preventive therapy.

Documento de consenso sobre la prevención y el tratamiento de la tuberculosis en pacientes candidatos a tratamiento biológico

Palabras clave:
Enfermedades inflamatorias crónicas
Infección tuberculosa latente
Terapias biológicas
Técnicas de liberación de interferón gamma

RESUMEN

El riesgo de enfermar de tuberculosis ha aumentado en los pacientes con enfermedades inflamatorias crónicas que reciben tratamiento inmunosupresor, en particular en aquellos tratados con terapia anti-TNF (del inglés *tumor necrosis factor*). En estos pacientes es obligatoria la detección de la infección tuberculosa latente y el tratamiento de dicha infección, dirigido a reducir el riesgo de progresión a enfermedad tuberculosa.

Este documento de consenso resume la opinión de expertos y los conocimientos actuales sobre tratamientos biológicos, incluidos los bloqueantes del TNF. Se establecen recomendaciones para la utilización de las técnicas de liberación de interferón-gamma (IGRA) y la prueba de la tuberculina (PT) para el diagnóstico y el tratamiento de la infección tuberculosa latente.

☆ Please cite this article as: Mir Viladrich I, Daudén Tello E, Solano-López G, López Longo FJ, Taxonera Samso C, Sánchez Martínez P, et al. Documento de consenso sobre la prevención y el tratamiento de la tuberculosis en pacientes candidatos a tratamiento biológico. Arch Bronconeumol. 2016;52:36–45.

☆☆ Consensus Document from the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), Spanish Academy of Dermatology and Venereology (AEDV), Spanish Society of Digestive Diseases (SEPD), Spanish Society of Rheumatology (SER) and Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC).

* Corresponding author.
E-mail address: imir@hsll.es (I. Mir Viladrich).

1579-2129/

Introduction

The development of biological therapies in the last decade has meant a definitive change in the treatment of chronic inflammatory diseases, which include rheumatoid arthritis (RA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), Crohn's disease (CD), ulcerative colitis (UC), psoriasis and psoriatic arthritis, among others. In 1998, the United States Food and Drug Administration (FDA)[1] approved the use of infliximab in patients resistant to conventional immunomodulatory treatment. Since then, more than 20 new drugs have been marketed for the treatment of immune-mediated inflammatory diseases (IMID), in which tumor necrosis factor (TNF) and TNF receptors play a key role in the immune response during acute and chronic inflammation processes.[2]

Pharmacovigilance of the first authorized biological agents (infliximab and etanercept) rapidly highlighted the emergence of cases of associated tuberculosis (TB).[3–5]

Several studies have shown that the diagnosis of latent tuberculosis infection (LTBI) in patients and its preventive treatment with isoniazid (INH) for 9 months reduce the likelihood of progression to active tuberculosis.[6,7] However, given that cases continue to be observed even after preventive treatment with INH, protocols must be reviewed and improvements in the sensitivity and specificity of diagnostic tests sought to improve the therapeutic approach to the IMID pacients.[8]

Rationale and Aims of the Document

A wealth of new information on biological therapies available for patients with IMID has emerged. This, together with a lack of guidelines from different Spanish scientific societies, justifies the publication of a consensus document based on scientific evidence and endorsed by a group of experts that can update existing information and previous recommendations. One of the main objectives of this document is to facilitate the diagnosis, treatment and follow-up of patients with LTBI who are candidates for biological therapies.

Methodology

This document has been drafted by a team of experts designated by various scientific societies. All members of the team specialize in the study and monitoring of patients who are candidates for biological therapies. Based on the information obtained, recommendations have been formulated based on the classification of the American Society of Infectious Diseases,[9] as per Table 1.

Biological Treatments in Rheumatic Diseases: Current Indications

Biological treatments have revolutionized the treatment of systemic autoimmune inflammatory diseases and spondyloarthritis. Before their introduction, only non-steroidal anti-inflammatory drugs (NSAID), glucocorticoids and so-called disease modifying drugs (DMD) were available which, in general, only slightly modified the natural evolution of RA. Today, disease progression can be halted and complete remission achieved in most patients. Tables 2 and 3 summarize the main drugs used in the treatment of rheumatic diseases and their current indications.[10–44]

Biological Treatments in Inflammatory Bowel Disease: Current Indications

Inflammatory bowel disease (IBD) includes 2 diseases, UC and CD, which are characterized by their chronic nature and alternation of outbreaks between periods of remission that vary in length.

The therapeutic goal includes rapid control of inflammatory activity during flare-ups, in order to improve symptoms and prevent complications that lead to structural damage in the digestive tract, with permanent incapacitating consequences. Once remission has been achieved, the aim of maintenance treatment is for the disease to remain inactive, and to prevent the onset of new outbreaks.

The main biological treatments for IBD and their indications are summarized in Table 4.[45–69]

Biological Treatments in Psoriasis: Current Indications

Today, the biological drugs used in the treatment of psoriasis (the only approved dermatological indication) are as follows: etanercept, infliximab, adalimumab and ustekinumab. The summary of product characteristics of these 4 drugs state that they have been approved for the "treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or who are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA".[70–73] Table 5 summarizes the indications for each biological drug in psoriasis.[70–77]

Tuberculosis Risk Associated With Biological Treatments

Tuberculosis infection is caused by the inhalation of viable bacilli which, in general, persist in an inactive state known as LTBI. These, however, can sometimes progress rapidly to active tuberculosis. Persons with LTBI remain asymptomatic and are not contagious. In most individuals, the initial infection by *Mycobacterium tuberculosis* is contained by the host's defenses, and remains latent. Nevertheless, this latent infection can become active disease at any time.

The risk of tuberculosis reactivation with anti-TNF depends on 2 variables: the immunomodulatory effect of treatment, and the prevalence of underlying tuberculosis infection in a particular population.

Treatment of the latent infection does not provide total protection,[78] and the existence of a standard period for reactivation has not been determined, as this varies according to the drug used.[79] The British Society for Rheumatology biologics register (BSRBR) detected an incidence of TB of 39 cases per 100 000 patients/year with etanercept, 103 cases per 100 000 with infliximab, and 171 cases per 100 000 with adalimumab.

Diagnostic Techniques for Latent Tuberculosis Infection: Usefulness in Immunosuppressed Patients

The investigation of possible tuberculosis infection among patients who are candidates for biological treatments should commence with evaluation of the potential risk of exposure to *M. tuberculosis*. The groups at highest risk are:

a. Persons who have had recent contact with tuberculosis patients.
b. Persons who are born or who reside in countries with a high prevalence of TB, or who travel frequently to these areas for business, family or humanitarian reasons.
c. Residents and workers in closed institutions, such as jails, homeless shelters or social-healthcare centers of all types.
d. Persons with a positive reaction to the tuberculin skin test (TST) who have not received specific treatment.
e. Persons who abuse alcohol or other toxic substances, while remembering also that TB is more common in smokers than in non-smokers.
f. Healthcare workers, particularly those who treat patients with active TB.

Table 1
Recommendations by Strength and Scientific Quality.[9]

Recommendations According to Categories of Strength	
A	Good evidence to support the recommendation
B	Moderate evidence to support the recommendation
C	Poor evidence that does not enable the recommendation to be either supported or rejected.
Recommendations According to Scientific Quality	
Grade I	Recommendation based on at least one well-designed, controlled, randomized clinical trial
Grade II	Recommendation based on at least one well-designed, but not randomized clinical trial, cohort studies, multiple time-series studies or very evident results in uncontrolled trials
Grade III	Recommendation based on the opinion of experts, descriptive studies or clinical experience

Table 2
Summary of the Main Biological Therapies Marketed.

Active Substance/ Commercial Name	Definition and Mechanisms of Action	Date of Authorization
Infliximab (Remicade®)	Anti-TNF-alpha chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant deoxyribonucleic acid (DNA) technology. It acts by blocking soluble TNF (sTNF) and transmembrane TNF (tmTNF). It induces apoptosis in peripheral monocytes and lamina propria T cells[10]	August 1999
Etanercept (Enbrel®)	Dimer constructed by fusing the soluble extracellular domain of human TNF receptor-2 and the Fc domain of human IgG1 using recombinant DNA techniques from a culture of Chinese hamster ovary (CHO) cells. It acts by blocking soluble TNF (sTNF) and, with less biological potency, transmembrane TNF (tmTNF)[10]	February 2000
Anakinra (Kineret®)	Human IL-1 receptor antagonist produced in *Escherichia coli* cells by recombinant DNA technology. It blocks IL-1 and competitively inhibits its binding to its receptor IL-1R1[12]	March 2002
Adalimumab (Humira®)	Anti-TNF-alpha recombinant human monoclonal antibody expressed in CHO cells. It acts by blocking soluble TNF (sTNF) and transmembrane TNF (tmTNF). It induces apoptosis in peripheral monocytes and lamina propria T cells[10]	September 2003
Rituximab (Mabthera®)	Chimeric murine/human monoclonal antibody obtained by genetic engineering of CHO cells and made up of a glycosylated Ig with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences. It acts by depleting the CD-20 positive lymphocyte population by apoptosis, cellular cytotoxicity and complement activation	June 2006
Abatacept (Orencia®)	IgG1-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fusion protein obtained by recombinant DNA technology in CHO cells. It has a high affinity for CD80/86, which inhibits the binding of CD28 to CD80, blocking the costimulation of T lymphocytes[13]	May 2007
Tocilizumab (RoActemra®)	Recombinant humanized, anti-human monoclonal antibody of the IgG1 class directed against IL-6 receptors, produced in CHO cells using recombinant DNA technology. It acts by blocking IL-6 with a reduction in the inflammatory response[11]	January 2009
Ustekinumab (Stelara®)	Fully human monoclonal antibody produced in a murine myeloma cell line using recombinant DNA technology. It inhibits both Th1 activation by IL-12 and Th17 activation by IL-23[14]	January 2009
Golimumab (Simponi®)	Human IgG1κ monoclonal antibody produced in a murine hybridoma cell line using recombinant DNA technology. It acts by blocking soluble TNF (sTNF) and transmembrane TNF (tmTNF)[10]	October 2009
Certolizumab pegol (Cimzia®)	Recombinant, humanized antibody Fab' fragment against TNF-alpha expressed in *Escherichia coli* and conjugated to polyethylene glycol. It acts by blocking soluble TNF (sTNF) and transmembrane TNF (tmTNF)[10]	October 2010
Belimumab (Benlysta®)	Human IgG1λ monoclonal antibody produced in a mammalian cell line (NS0) using recombinant DNA technology	July 2011

g. Patients with radiological lesions suggestive of old TB, especially if they have never received treatment, as is the case of persons with a positive tuberculin test.
h. Typically, also individuals at the extremes of life, those with immunosuppressive diseases and other comorbidities that have been related with a higher risk of TB. These conditions include not only HIV infection, autoimmune diseases and post-transplantation, but also lung diseases (silicosis), chronic renal failure, gastrectomy, diabetes and some tumors, such as head and neck cancers.

Current Clinical Practice

In the absence of a reference test for the diagnosis of tuberculosis infection, current management of patients with autoimmune diseases who are candidates for treatment with anti-TNF drugs includes taking the patient's medical history (aimed at discovering any history of TB or latent infection, previously treated or untreated), looking for evidence of previous TB on the chest X-ray, and performing a TST.

The TST consists of measuring the delayed hypersensitivity reaction that occurs on the skin after intradermal inoculation of the purified protein derivative (PPD), a mixture of more than 200 *M. tuberculosis* proteins. Given that the antigens contained in the PPD are also found in other mycobacteria, vaccination with BCG can be a cause of false positives in the TST. Furthermore, the sensitivity of the TST is affected in patients receiving immunosuppressive treatment, in which a high percentage of false negatives has been observed.[80,81] In this respect, some studies in patients with RA have shown a rate of false positive TSTs as high as 40%.[82] A repeat TST is sometimes recommended to increase sensitivity due to the booster effect on false negatives, but this also reduces its specificity by increasing the number of false positives due to the BCG vaccination and exposure to non-tuberculous mycobacteria.[83]

Diagnostic Techniques Based on Interferon-Gamma Release

Genome sequencing of *M. tuberculosis* has improved identification of the genes involved in its pathogenesis and revealed the presence of genetically different regions. *M. tuberculosis* proteins

Table 3
Summary of Biological Therapies in Rheumatic Diseases.

Drugs	Primary Indication(s)	Observations	Other Indications
Infliximab (Remicade®)	Adults with RA,[15,16] active PA,[17,18] AS[19]	When response to DMDs has been inadequate or in severe, progressive disease with methotrexate if no intolerance	Has been successfully used in uveitis, Behçet's disease[20,21]
Etanercept (Enbrel®)	Adults with RA,[22] JIA,[23] moderately or severely active PA.[24] In children >2 years with polyarticular or oligoarticular JIA, juvenile PA,[25] AS[26]	When response to DMDs has been inadequate or in severe, progressive disease	
Anakinra (Kineret®)	Adults with RA[27]	Of limited use due to its adverse effects	
Adalimumab (Humira®)	In RA,[28,30] polyarticular JIA,[30] moderately or severely active PA.[31] AS or severely active undifferentiated spondyloarthritis[32]	In combination with methotrexate and when response to DMDs has been inadequate or in severe, progressive disease	
Rituximab (Mabthera®)	Adults with severe active RA[33]	Patients with inadequate response or intolerance to DMDs or TNF inhibitors. Patients with positive rheumatoid factor and/or cyclic citrullinated peptide antibodies have a better response than negative patients. Repeated cycles every 6 months maintain the improvement	In adults with non-Hodgkin's lymphoma or chronic lymphocytic leukemia and, off-label, in the treatment of ITP, other autoimmune thrombopenias, systemic vasculitis, cryoglobulinemias associated with HCV or HIV, SLE, polymyositis and other systemic autoimmune inflammatory diseases[34,35]
Abatacept (Orencia®)	In RA and polyarticular JIA in >6 years with moderately or severely active disease	In combination with methotrexate and when response to DMDs or TNF-alpha antagonists has been inadequate[36,37]	
Tocilizumab (RoActemra®)	In RA, systemic JIA with moderately to severely active disease in adults[38] and children[39]	When response to DMDs or TNF-alpha antagonists has been inadequate or in severe cases as first line treatment after methotrexate	
Golimumab (Simponi®)	In severe, progressive RA,[40] PA[41] and AS[42]	No response with NSAID or DMDs or directly in cases of severe, progressive RA or PA	
Certolizumab pegol (Cimzia®)	In moderate or severe RA[43]	In combination with methotrexate and when the response to DMDs has been inadequate	
Belimumab (Benlysta®)	As add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (positive anti-dsDNA and low complement) despite standard therapy	Evaluated in randomized, double-blind, placebo-controlled studies, although patients with severe active lupus nephritis or severe active neuropsychiatric manifestations were excluded[44]	

AS, ankylosing spondylitis; DMDs, disease-modifying drugs; ITP, idiopathic thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; PA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

(ESAT-6 and CFP-10) are encoded in the region known as RD1, and behave as specific antigens. In persons infected by *M. tuberculosis*, these induce a type Th-1 immune response with production of interferon gamma (IFN-γ). This region, absent in all strains of *M. bovis*-BCG and in almost all non-tuberculous mycobacteria (except for *M. kansasii*, *M. marinum* and *M. szulgai*), is present in all known virulent strains of *M. tuberculosis.*

Interferon-gamma release assays (IGRA) are based on the detection, in the peripheral blood of infected individuals, of IFN-γ released by sensitized T cells in response to *in vitro* stimulation with *M. tuberculosis*-specific antigens.

There are two commercial kits available:

a. QuantiFERON®-TB-Gold (Cellestis Ltd., Carnegie, Australia),[84] which determines the total IFN-γ production in individuals infected by *M. tuberculosis* using an ELISA technique. A value greater than or equal to 0.35 IU/ml is considered positive.
b. T-SPOT.TB® (Oxford Immunotec Ltd., United Kingdom), developed by A. Lalvani in the late nineties.[85] This is a more laborious procedure that requires monocytes to be separated before incubating them with the ESAT-6 and CFP-10 antigens. It is read using the ELISPOT technique, in which each spot represents an IFN-γ-secreting T cell. The result is considered positive when there are ≥6 spots.

Both techniques include positive and negative controls that can detect false results due to anergy or immunological problems (reported as 'indeterminate' results).[86] When results are inconclusive (more common in IMID), most guidelines recommend repeating the test, which in many cases confirms the negative result.[87,88]

IGRA techniques have several advantages over the TST:

a. They eliminate subjectivity in the interpretation of results.
b. The test can be repeated if necessary.
c. There is no need for the patient to return 48–72 h later for the results to be read.
d. They are easy to standardize and apply in the laboratory.
e. They enable anergic patients to be detected.
f. They respect the patient's privacy.

Disadvantages include the cost, which is higher than that of the TST.

Table 4
Summary of Biological Therapies in Intestinal Diseases.

Biological Drugs	Indications and Observations		
Infliximab (Remicade®)	Moderately to severely active CD[45]	The benefit translates into a saving in corticosteroid use,[45,46] a reduction in hospitalization and surgery rates[47,48] and better patient-perceived quality of life.[47,49] Systematic treatment has demonstrated its ability to induce mucosal healing in CD[52]	In adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or immunomodulators; or who are intolerant to or have medical contraindications for such therapies
	Fistulizing, active CD[46]		
	Moderately to severely active UC[51]	Shows effectiveness and improves quality of life in the short and long term in patients with UC[52]	
	Active CD or UC in children[53]	Infliximab has been shown to be effective and induces an improvement in quality of life and height in children, as well as a significant reduction in corticosteroid use	
	Infliximab has been effective in situations not listed in the summary of product characteristics, such as the prevention of post-operative recurrence of CD after ileal resection,[54] pouchitis in patients with UC and colectomy[55] and the pyoderma gangrenosum associated with IBD[56]		
Adalimumab (Humira®)	Moderately to severely active CD[57,58]	Adalimumab has demonstrated its efficacy and safety in the induction and maintenance of remission in CD and its benefit translates into a reduction in hospitalization and surgery rates.[59] Its use has demonstrated its ability to induce mucosal healing in CD[60]	In adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant or have contraindications to such therapies
	Moderately to severely active UC[61,62]	In these patients, it reduced the need for hospital admission at 52 weeks, for both all cause hospitalizations and UC-related hospitalisations[63]	
	Severely active CD in pediatric patients (>6 years)	In those who present an insufficient response to conventional therapy, including primary nutrition therapy, a corticosteroid and an immunomodulator, or who are intolerant to or have contraindications for such therapies[64]	
	Adalimumab has been shown to be useful in situations not considered in the summary of product characteristics, such as the prevention of postoperative recurrence of CD after ileal resection[65]		
Golimumab (Simponi®)	Moderately to severely active UC	In adult patients who have had an inadequate response to conventional therapy, including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant or have contraindications to such therapies	
	Golimumab induces mucosal healing and improves quality of life compared to placebo,[66] and maintains a sustained clinical response up to week 52.[67] The safety data from both studies are similar to those of other anti-TNFs or studies on golimumab for other indications		
Certolizumab pegol (Cimzia®)	Moderate to severe CD	For induction and maintenance of the response in patients with an inadequate response to conventional medication	The drug is approved for this use in the United States and Switzerland, but not in other European countries. Approved by the FDA but not by the EMA
	The efficacy of certolizumab pegol was evaluated in 2 randomized, double-blind, placebo-controlled clinical trials.[68,69] One of the reasons for refusing authorization by the EMA is due to the short duration of the maintenance studies		

CD, Crohn's disease; EMA, European Medicines Agency; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Interpretation of Results in Patients Who Are Candidates for Biological Treatments

IGRA techniques are used as routine tests for the diagnosis of LTBI in the United States, Canada, Australia, Japan, and in some western European countries (United Kingdom, Italy, Germany, Switzerland). Some countries use them instead of the TST, while others combine both tests. In Spain, it is recommended that the TST be complemented with an IGRA technique in persons who are candidates for treatment if they have been vaccinated with BCG (to rule out a false positive tuberculin test), and in those with a negative skin test and suspected immunosuppression (to rule out a false negative tuberculin test).[89,90]

Despite numerous studies published in recent years, data on the diagnostic yield of these tests in patients with IMID are limited and controversial.[80,89,91–94] According to published studies:

Table 5
Summary of Biological Therapies in Dermatological Diseases.

Biological Drugs	Indications and Observations
Etanercept (Enbrel®)	Adults with psoriasis. Indication: treatment of adults with moderate to severe plaque psoriasis who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy, including cyclosporine, methotrexate or psoralen and ultraviolet light (PUVA).[71,74] Approved by the EMA in 2004 Pediatric psoriasis. Indication: treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.[71,74] Approved by the EMA in 2009
Infliximab (Remicade®)	Adults with psoriasis. Indication: treatment of moderate to severe plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy, including cyclosporine, methotrexate or PUVA[72,75]
Adalimumab (Humira®)	Adults with psoriasis. Indication: treatment of chronic moderate to severe plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy, including cyclosporine, methotrexate or PUVA.[70] Approved by the EMA in 2007
Ustekinumab (Stelara®)	Adults with psoriasis. Indication: treatment of moderate to severe plaque psoriasis in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy, including cyclosporine, methotrexate and PUVA.[73,77] Approved by the EMA in 2009

EMA, European Medicines Agency.

(a) concordance between the TST and IGRA tests is weaker in patients with systemic inflammatory diseases than in healthy subjects, due to the lower prevalence of positive tuberculin tests among the former[82,95–100]; (b) the magnitude of the tuberculin response is significantly lower in patients with IMID than in healthy controls[82]; (c) in vaccinated individuals, a discrepancy has been observed between a positive TST and a negative result in an IGRA test; and (d) in patients receiving corticosteroid treatment, a discrepancy is often observed between a negative TST and a positive IGRA test.[96]

Due to the vulnerability of these patients to TB while receiving anti-TNF treatment, it would seem prudent to perform both tests (IGRA and TST) in parallel in order to maximize the diagnostic sensitivity of screening, at least until evidence of the usefulness of IGRA techniques in this population has been established.[88] It is important to mention that when both tests are performed sequentially, the IGRA tests should be performed first, to prevent the booster effect caused by the TST.[101,102] It is not known how long this effect persists, or whether it depends on the amount of PPD administered or its characteristics.

The results of IGRA tests in patients on anti-TNF treatment remain difficult to interpret. Data from recent studies[103–105] show conversions and reversions in both tests, which are related with reproducibility problems and changes in patients' immune status. This variability means that it is not advisable to repeat the tests for patient's follow-up during treatment.

Treatment of Latent Tuberculosis Infection: Treatment Guidelines

The identification and treatment of LTBI reduces the likelihood of reactivation in these patients, thereby protecting their health and that of other people in their environment by reducing the number of possible sources of infection.[106,107] Treatment of latent infection should only be initiated once active TB has been excluded.

LTBI treatment regimens include INH for 9 months, rifampicin (RIF) alone for 4 months, or INH with RIF for 3 months.[108]

Isoniazid. The usual dose is 5 mg/kg/day, with a maximum of 300 mg daily in adults. The only study to compare the efficacy of different durations of INH treatment showed an efficacy of 65% in the 6 month regimen, while in the 12 month regimen the efficacy was 75% (not significantly different from the former).[109] Extrapolating the data from randomized trials shows that the optimal duration of INH treatment for LTBI is 9 months.[109,110] The major side effect of INH is hepatitis, with an incidence of 1 case in every 1000 persons.[111]

Rifampicin. The usual dose is 10 mg/kg/day, with a maximum of 600 mg daily. The efficacy of RIF in reducing the incidence of active TB is thought to be similar to that of INH.[112,113] Although little data is available, RIF appears to be well tolerated, with a low rate of hepatotoxicity.[112]

Isoniazid and Rifampicin. There is little data on the use of the combination of INH and RIF in HIV-negative patients, but some studies have shown that it is an effective regimen, with good adherence and well tolerated.[114] A meta-analysis of small studies conducted in the non-HIV population concluded that it is equally effective and no more toxic.[115]

Treatment of Latent Tuberculosis Infection in Patients Who Are Candidates for Biological Therapies

The United States Center for Disease Control and Prevention (CDC) recommends treatment of LTBI in patients scheduled to start treatment with a TNF inhibitor and who have a positive TST ($\geq$5 mm induration) or a positive IGRA test, regardless of whether they have been vaccinated with BCG (as its effect on the TST is greatly attenuated over time).[116–118] It is also recommended in the case of patients with negative TST or IGRA in whom there is evidence of untreated tuberculosis on the chest X-ray, or epidemiological evidence of previous exposure to TB (for example, after having been in close contact with a person infected with TB or having resided in a country with a high incidence of TB).

In general, candidates for anti-TNF who are indicated for LTBI treatment receive standard treatment, *i.e.* INH for 9 months. The recommended duration of LTBI therapy before starting a TNF inhibitor is not well established, but most authors propose that, whenever possible, patients receive LTBI therapy for at least 1 month before starting the anti-TNF regimen.[8,119]

Treatment of the latent infection with INH will not protect the patient against reactivation of the infection by INH-resistant strains.[120] RIF is indicated in the case of patients who are intolerant to INH, or whose index cases present strains resistant to INH but sensitive to RIF.

Recommendations of the Consensus Document

The recommendations summarized here are based on evidence published up to 2013, on various national guidelines, and on the opinions of experts specializing in the treatment of patients with IMID who may be candidates for receiving biological treatment.

These recommendations are:

1. All patients who are candidates for biological treatment should be studied to detect a possible LTBI, given that they constitute one of the groups at highest risk of developing tuberculosis (AII).

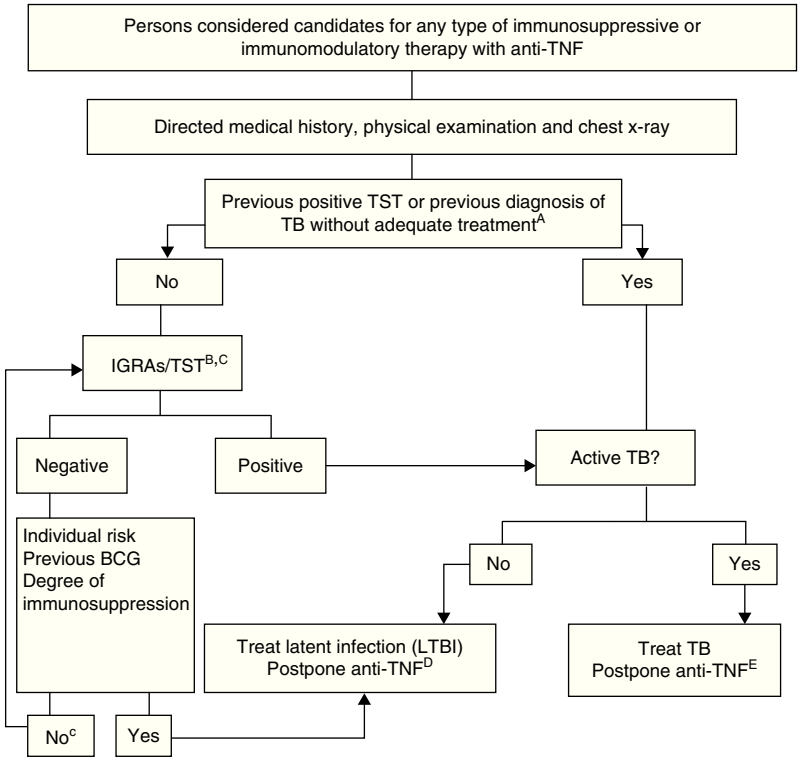

Fig. 1. Action algorithm for evaluating tuberculosis infection in patients who are candidates for anti-TNF treatments. For interpretation of determinants A, B, C, D and E, see text.

2. The risk of these patients for developing the disease is related with the anti-TNF drug used. Infliximab and adalimumab are associated with the highest risk (AIII).
3. Methods for diagnosing LTBI are based on:
   - Review of the patient's medical record to show a history of TB or contact with patients with active TB.
   - Evidence of possible old tuberculous lesions on the chest X-ray. In case of doubt, the study should be completed with a chest computed tomography (CT) scan, which is more accurate than conventional radiology in detecting early radiological signs of active TB or old lesions.
   - Simultaneous performance of IGRA tests and a TST. A positive result in any of these tests is considered indicative of LTBI (AIII).
4. False negative results in the TST and IGRA tests are more common in patients diagnosed with IMID (AIII).
5. Repeating the TST (booster effect) has not been shown to improve the sensitivity of the test in IMIDs, and reduces its specificity; therefore, it is not currently recommended, as IGRA techniques are available (CIII).
6. Blood for IGRA tests should be extracted before the TST, due to the booster effect identified on IGRA tests (AIII).
7. The specificity and sensitivity of both IGRA techniques for the diagnosis of LTBI is similar in patients with IMID, although the sensitivity of the T-SPOT.TB is somewhat greater in patients treated with corticosteroids. Its use should therefore be assessed in these patients (BIII).
8. Indeterminate results in IGRA tests should always be confirmed with a second test, which is usually negative in most cases (AIII).
9. A negative result in the TST and IGRA tests does not rule out the presence of an LTBI (AIII).
10. Preventive treatment is recommended in all candidates for biological therapies who present positive results in any diagnostic test for LTBI, once active TB has been excluded (AII).
11. The recommended treatment regimen is INH for 9 months. In exceptional cases only, treatment with INH+RIF for 3 months may be indicated (AIII).
12. Treatment should be monitored each month. In the event of INH-induced hepatotoxicity, an alternative regimen with RIF for 4 months is recommended (AIII).
13. Treatment of the LTBI for 4 weeks is considered safe (by most experts) for initiating anti-TNF treatment (AIII).
14. According to current data, study and screening of the LTBI after the start of and during anti-TNF treatment are not indicated as a strategy for diagnosing initial false negatives. The screening study should only be repeated if there are changes in the clinical symptoms or after possible exposure to *M. tuberculosis* on travel to highly endemic areas (AIII).
15. If the patient is diagnosed with active tuberculosis, anti-TNF treatment should be suspended and not re-started until the entire anti-tuberculosis treatment cycle has been completed. There is no evidence that the duration of treatment of the disease due to TB should be modified in this context (AIII).
16. The risk of relapse in patients who have correctly completed tuberculosis treatment does not seem to be higher after starting anti-TNF treatment (AIII).

Fig. 1 shows the proposed algorithm for evaluating tuberculosis in patients who are candidates for biological treatments,[121] in which the following determinants were used:

A. Adequate treatment of the TB is defined as ≥6 months of therapy with first line drugs, and includes ≥2 months with the combination RIF+INH+pyrazinamide+ethambutol. Latent infection can be adequately treated with 9 months of INH, 3 months of INH+RIF or 4 months of RIF alone.
B. The risk of latent infection is derived from considering factors such as known exposure to a contagious case, age, country of

origin, and work and social history, including travel to endemic countries and repeated exposure to risk groups (closed institutions, homeless persons, drug users).

C. In persons who have been LTBI carriers for many years, the TST can be negative and become positive in a second TST (booster phenomenon). A second test is not recommended due to the availability of IGRA techniques. The study should only be repeated according to recommendation no. 14.

D. There are no conclusive data that allow a safe period to be established between the start of treatment of the latent infection and the start of anti-TNF treatment. Most experts consider that a delay of 4 weeks is a safe standard practice.

E. Treatment of the active TB must be completed before initiating the biological treatment.

Conflicts of Interests

Esteban Daudén Tello declares that he is a member of an advisory board, a consultant, has received grants and research grants, has participated in clinical trials, and has received honoraria as a speaker from the following pharmaceutical companies: AbbVie (Abbott), Amgen, Janssen-Cilag, Leo Pharma, MSD, Pfizer, Novartis, Celgene and Lilly.

Carlos Taxonara Samso declares that he has been a consultant and speaker for MSD and AbbVie.

Francisco Javier López Longo declares occasional contracts as a speaker with AbbVie, Actelion, Bristol-Myers-Squibb, GSK, MSD, Pfizer, Roche Farma and UCB, and has received research funding from AbbVie and GSK.

The other authors declare that they have no conflict of interests.

References

1. Infliximab approval process in Crohn's disease. Department of Health and Human Services, Public Health Service, Food and Drug Administration; 1998.
2. Furst DE, Keystone EC, Fleischmann R, Mease P, Breedveld FC, Smolen JS, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. Ann Rheum Dis. 2010;69:12–29.
3. 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.
4. 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.
5. Obrador A, Lopez San Roman A, Munoz P, Fortun J, Gassull MA. Consensus guideline on tuberculosis and treatment of inflammatory bowel disease with infliximab. Spanish Working Group on Crohn Disease and Ulcerative Colitis. Gastroenterol Hepatol. 2003;26:29–33.
6. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003;3:148–55.
7. 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.
8. Jauregui-Amezaga A, Turon F, Ordás I, Gallego M, Feu F, Ricart E, et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. J Crohns Colitis. 2013;7:208–12.
9. Gross PA, Barrett TL, Dellinger P, Krause PJ, Martone WJ, McGowan JE, et al. Purpose of quality standards for infectious diseases. Clin Infect Dis. 1994;18:421.
10. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonists mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117:92–101.
11. Fonseca JE, Santos MJ, Canhao H, Choy E. Interleukin-6 as a key player in systemic inflammation and joint destruction. Autoimmun Rev. 2009;8:538–42.
12. Rosman Z, Shoenfeld Y, Zandman-Goddard G. Biologic therapy for autoimmune diseases: an update. BMC Med. 2013;11:88.
13. Pieper J, Herrath J, Raghavan S, Muhammad K, van Vollenhoven R, Malmström V. CTLA4-Ig (abatacept) therapy modulates T cell effector functions in autoantibody-positive rheumatoid arthritis patients. BMC Immunol. 2013;14:34.
14. Benson JM, Peritt D, Scallon BJ, Heavner GA, Shealy DJ, Giles-Komar JM, et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. MAbs. 2011;3:535–45.
15. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932–9.
16. 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.
17. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). ArthritisRheum. 2005;52:1227–36.
18. Hoff M, Kavanaugh A, Haugeberg G. Hand bone loss in patients with psoriatic arthritis: posthoc analysis of IMPACT II data comparing infliximab and placebo. J Rheumatol. 2013;40:1344–8.
19. Van der Heijde D, Dijkmans B, Geusens P, Sieper J, deWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52:582–91.
20. Cantini F, Niccoli L, Nannini C, Kaloudi O, Cassarà E, Susini M, et al. Efficacy of infliximab in refractory Behçet's disease-associated and idiopathic posterior segmentuveitis: a prospective, follow-up study of 50 patients. Biologics. 2012;6:5–12.
21. Okada AA, Goto H, Ohno S, Mochizuki M, for Ocular Behçet's disease research group of Japan. Multicenter study of infliximab for refractory uveoretinitis in Behçet disease. Arch Ophthalmol. 2012;130:592–8.
22. Moreland LW, Weinblatt ME, Keystone EC, Kremer JM, Martin RW, Schiff MH, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. Arthritis Rheum. 2008;59:32–861.
23. Lovell DJ, Reiff A, Jones OY, Schneider R, James N, Stein LD, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2006;54:1987–94.
24. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004;50:2264–72.
25. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2013:1–9.
26. Brandt J, Listing J, Haibel H, Sorensen H, Schwebig A, Rudwaleit M, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology. 2005;44:342–8.
27. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicenter double-blind randomized placebo-controlled trial of Kineret® (anakinra), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate therapy. Ann Rheum Dis. 2004;63:1062–8.
28. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor a monoclonal antibody for the treatment of RA in patients taking concomitant methotrexate. The ARMADA trial. Arthritis Rheum. 2003;48:35–45.
29. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhovenet R, et al. The PREMIER study: combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in methotrexate-naïve patients with early, aggressive rheumatoid arthritis. Arthritis Rheum. 2006;54:26–37.
30. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359:810–20.
31. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EHS, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. ADEPT. Arthritis Rheum. 2005;52:3279–89.
32. Van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BAC, Braun J, et al. Long-term efficacy and safety in Ankylosing Spondylitis Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ATLAS). Arthritis Rheum. 2006;54:2136–46.
33. Gomez-Reino JJ, Maneiro JR, Ruiz J, Roselló R, Sanmarti R, Romero AB, et al. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis. 2012;71:1861–4.
34. López-Longo FJ. Rituximab en el lupus eritematoso sistémico y otras enfermedades autoinmunes. Med Clin Monogr. 2008;9:15–9.
35. Fernandez-Nebro A, Marenco de la Fuente JL, Carreño L, Galindo Izquierdo M, Tomero E, Rúa-Figueroa I, et al. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus. 2012;21:1063–76.
36. 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.
37. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: A randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372:383–91.

38. Fleischmann RM, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. J Rheumatol. 2013;40:113–26.
39. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385–95.
40. Smolen JS, Kay J, Doyle MK, Landewé 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.
41. Wagner CL, Visvanathan S, Elashoff M, McInnes IB, Mease PJ, Krueger GG, et al. Markers of inflammation and bone remodelling associated with improvement in clinical response measures in psoriatic arthritis patients treated with golimumab. Ann Rheum Dis. 2013;72:83–8.
42. Braun J, Baraliakos X, Hermann KG, Deodhar A, van der Heijde D, Inman R, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis. 2014;73:1107–13.
43. Van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. American College of Rheumatology hybrid analysis of certolizumab pegol plus methotrexate in patients with active rheumatoid arthritis: data from a 52-week phase III trial. Arthritis Care Res. 2011;63:128–34.
44. Petri MA, van Vollenhoven RF, Buyon J, Levy RA, Navarra SV, Cervera R, et al. Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III Belimumab trials. Arthritis Rheum. 2013;65:2143–53.
45. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology. 2004;126:402–13.
46. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulising Crohn's disease. N Engl J Med. 2004;350:876–85.
47. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. Am J Gastroenterol. 2004;99:91–6.
48. Lichtenstein GR, Yan S, Bala M, Blank M, Sands B. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulising Crohn's disease. Gastroenterology. 2005;128:862–9.
49. Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol. 2003;98:2232–8.
50. Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63:433–42.
51. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
52. Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. Am J Gastroenterol. 2007;102:794–802.
53. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007;132:863–73.
54. Hyams J, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391–9.
55. Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009;136:441–50.
56. Viazis N, Giakoumis M, Koukouratos T, Anastasiou J, Katopodi K, Kechagias G, et al. Long term benefit of one year infliximab administration for the treatment of chronic refractory pouchitis. J Crohns Colitis. 2013;7:457–60.
57. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, Panaccione R, et al. Adalimumab for maintenence treatment of Crohn's disease: results of the CLASSIC II trial. Gut. 2007;56:1232–9.
58. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007;132:52–65.
59. Feagan BG, Panaccione R, Sandborn WJ, D'Haens GR, Schreiber S, Rutgeerts PJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology. 2008;135:1493–9.
60. Rutgeerts P, van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. Gastroenterology. 2012;142:1102–11.
61. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780–7.
62. Sandborn WJ, van Assche G, Reinisch W, Colombel FJ, d'Haens G, Douglas C. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257–65.
63. Feagan BG, Sandborn WJ, Lazar A, Roopal B, Thakkar Huang B, Reilly N, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. Gastroenterology. 2014;146:110–8.
64. Hyams JS, Griffiths A, Markowitz J, Baldassano RN, Faubion WA, Colletti RB, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. Gastroenterology. 2012;143:365–74.
65. Savarino E, Bodini G, Dulbecco P, Assandri L, Bruzzone L, Mazza F, et al. Adalimumab is more effective than azathioprine and mesalamine at preventing postoperative recurrence of Crohn's disease: a randomized controlled trial. Am J Gastroenterol. 2013;108:1731–42.
66. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:85–95.
67. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:96–109.
68. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med. 2007;357:228–38.
69. Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OØ, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007;357:239–50.
70. European Medicines Agency. Ficha técnica de Humira (adalimumab). Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf [accessed 29.10.13].
71. European Medicines Agency. Ficha técnica de Enbrel (etanercept). Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf [accessed 29.10.13].
72. European Medicines Agency. Ficha técnica de Remicade (infliximab). Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf [accessed 29.10.13].
73. European Medicines Agency. Ficha técnica de Stelara (ustekinumab). Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf [accessed 29.10.13].
74. Ara M, Dauden E. Etanercept for the treatment of psoriasis. Expert Rev Dermatol. 2013;8:357–72.
75. Rott S, Mrowietz U. The use of infliximab in dermatology. J Dtsch Dermatol Ges. 2007;5:655–60.
76. Warren RB, Griffiths CE. The future of biological therapies. Semin Cutan Med Surg. 2010;29:63–6.
77. Tsuda K, Yamanaka K, Kondo M, Matsubara K, Sasaki R, Tomimoto H, et al. Ustekinumab improves psoriasis without altering T cell cytokine production, differentiation, and T cell receptor repertoire diversity. PLoS ONE. 2012;7:e51819.
78. Sichletidis L, Settas L, Spyratos D. TB in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006;10:1127–32.
79. Hamilton C. TB in the cytokine era: what rheumatologist need to know. Arthritis Rheum. 2003;48:2085–91.
80. García-Gasalla M, Fernández-Baca V, Mas AJ, Payeras-Cifre A, Cifuentes-Luna C, Taberner-Ferrer R, et al. Use of Quantiferon-TB-Gold in Tube® test for detecting latent tuberculosis in patients considered as candidates for anti-TNF therapy in routine clinical practice. Enferm Infecc Microbiol Clin. 2013;31:76–81.
81. Ponce de Leon D, Acevedo-Vasquez E, Sanchez-Torres A, Cucho M, Alfaro J, Perich R. Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. Ann Rheum Dis. 2005;64:1360–1.
82. Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J, et al. Comparison of an interferon-γ assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. J Rheumatol. 2008;35:776–81.
83. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. Clin Infect Dis. 1993;17:968–75.
84. Cellestis. Quantiferon-TB Gold; 2009. Available from: http://www.cellestis.com/ [accessed 20.10.09].
85. Oxford Immunotec. T.Spot-TB; 2009. Available from: http://www.oxfordimmunotec.com/ [accessed 20.10.09].
86. Dominguez J, De Souza-Galvao M, Ruiz-Manzano J, Latorre I, Prat C, Lacoma A, et al. Comparison of two commercially available gamma-interferon blood tests for immunodiagnosis of tuberculosis. Clin Vaccine Immunol. 2008;15:168–71.
87. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using interferon g release assays to detect *Mycobacterium tuberculosis* infection – United States, 2010. MMWR Recomm Rep. 2010;59:1–25.
88. European Centre for Disease Prevention and Control (ECDC). Use of interferon-gamma release assays in support of TB diagnosis. Available from: http://ecdc.europa.eu/en/publications/Publications/1103_GUI_IGRA.pdf [accessed July 2013].
89. Santin M, Muñoz L, Rigau D. Interferon-γ release assay for the diagnosis of tuberculosis and tuberculosis infection in HIV-infected adults: a systematic review and meta-analysis. PLoS ONE. 2012;7:e32482.
90. Ruiz Manzano J, Blanquer R, Calpe JL, Caminero JA, Caylá J, Dominguez JA, et al. Normativa SEPAR. Diagnóstico y tratamiento de la tuberculosis. Arch Bronconeumol. 2008;44:551–66.
91. Greenberg JD, Reddy SM, Schloss SG, Kurucz OS, Bartlett SJ, Abramson SB, et al. Comparison of an in vitro tuberculosis interferon-γ assay with delayed-type

hypersensitivity testing for detection of latent *Mycobacterium tuberculosis*: a pilot study in rheumatoid arthritis. J Rheumatol. 2008;35:770–5.
92. Inanc N, Aydin SZ, Karakurt S, Atagunduz P, Yavuz S, Direskeneli H. Agreement between Quantiferon-TB gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2009;36:2675–81.
93. Bocchino M, Matarese A, Bellofiore B, Giacomelli P, Santoro G, Balato N, et al. Performance of two commercial blood IFN-gamma release assays for the detection of *Mycobacterium tuberculosis* infection in patient candidates for anti-TNF-alpha treatment. Eur J Clin Microbiol Infect Dis. 2008;27:907–13.
94. Pratt A, Nicholl K, Kay L. Use of QuantiFERON TB Gold test as a part of a screening programme in patients with RA under consideration for treatment with anti-TNF-alpha agents: the Newcastle (UK) experience. Rheumatology. 2007;46:1035–6.
95. Takahashi H, Shigehara K, Yamamoto M, Suzuki C, Naishiro Y, Tamura Y, et al. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. Rheumatol Int. 2007;27:1143–8.
96. Vassilopoulos D, Stamoulis N, Hadziyannis E, Archimandritis AJ. Usefulness of enzyme-linked immunospot assay (Elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment. J Rheumatol. 2008;35:1464.
97. Matulis G, Juni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases performance of a *Mycobacterium tuberculosis* antigen specific IFN-gamma assay. Ann Rheum Dis. 2008;67:84–90.
98. Cobanoglu N, Ozcelik U, Kalyoncu U, Ozen S, Kiraz S, Furcan N. Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. Int J Tuberc Lung Dis. 2007;11:117–82.
99. Sellam J, Hamdi H, Roy C, Baron G, Leman M, Puechal X. Comparison of in vitro-specific blood tests with tuberculin skin test for diagnosis of latent tuberculosis before anti-TNF therapy. Ann Rheum Dis. 2007;66:1610–5.
100. Dominguez J, Latorre I, Altet N, Mateo L, de Souza Galvao ML, Ruiz-Manzano J, et al. IFN-gamma release assay to diagnose TB infection in the immunocompromised individual. Expert Rev Respir Med. 2009;3:309–27.
101. Van Zyl-Smit RN, Pai M, Peprah K, Meldau R, Kieck J, Juritz J, et al. Within-subject variability and boosting of T-cell interferon-gamma responses after tuberculin skin testing. Am J Respir Crit Care Med. 2009;180:49–58.
102. Vilaplana C, Ruiz-Manzano J, Gil O, Cuchillo F, Montane E, Singh M, et al. The tuberculin skin test increases the responses measured by T cell interferon-gamma release assays. Scand J Immunol. 2008;67:610–7.
103. Papay P, Primas C, Eser A, Novacek G, Winkler S, Frantal S, et al. Retesting for latent tuberculosis in patients with inflammatory bowel disease treated with TNF-a inhibitors. Aliment Pharmacol Ther. 2012;36:858–65.
104. Chen DY, Shen GH, Chen YM, Chen HH, Hsieh CW, Lan JL. Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFa inhibitors: the utility of IFNg assay. Ann Rheum Dis. 2012;71:231–7.
105. Hatemi G, Melikoglu M, Ozbakir F, Tascilar K, Yazici H. Quantiferon-TB Gold in tube assay for the screening of tuberculosis before and during treatment with tumor necrosis factor-alpha antagonists. Arthritis Res Ther. 2012;14:R147.
106. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000;161:S221–47.
107. Horsburgh CR Jr, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. N Engl J Med. 2011;364:1441.
108. Centers for Disease Control and Prevention (CDC), American Thoracic Society. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection – United States, 2003. MMWR Morb Mortal Wkly Rep. 2003;52:735.
109. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ. 1982;60:555.
110. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis. 1999;3:847.
111. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999;281:1014.
112. Villarino ME, Ridzon R, Weismuller PC, Elcock M, Maxwell RM, Meador J, et al. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. Am J Respir Crit Care Med. 1997;155:1735.
113. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008;149:689.
114. Jiménez-Fuentes MA, de Souza-Galvao ML, Mila Augé C, Solsona Peiró J, Altet-Gómez MN. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. Int J Tuberc Lung Dis. 2013;17:326–32.
115. Pho MT, Swaminathan S, Kumarasamy N, Losina E, Ponnuraja C, Uhler LM, et al. The cost-effectiveness of tuberculosis preventive therapy for HIV-infected individuals in southern India: a trial-based analysis. PLoS ONE. 2012;7:e36001.
116. Paluch-Oleś J, Magryś A, Kozioł-Montewka M, Koszarny A, Majdan M. Identification of latent tuberculosis infection in rheumatic patients under consideration for treatment with anti-TNF-α agents. Arch Med Sci. 2013;9:112–7.
117. Nordgaard-Lassen I, Dahlerup JF, Belard E, Gerstoft J, Kjeldsen J, Kragballe K, et al. Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment. Dan Med J. 2012;59:C4480.
118. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald. JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. Thorax. 2002;57:804–9.
119. Casas S, Andreu A, Juanola X, Bordas X, Alcaide F, Moure R, et al. Diagnosis of tuberculosis infection by tuberculin skin test and a whole-blood interferon-γ release assay in patients considered for anti-tumor necrosis factor-α therapy. Diagn Microbiol Infect Dis. 2011;71:57–65.
120. Fraser A, Paul M, Attamna A, Leibovici L. Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. Int J Tuberc Lung Dis. 2006;10:19–23.
121. Winthrop KL, Weinblatt ME, Daley CL. You can't always get what you want, but if you try sometimes (with two tests – TST and IGRA – for tuberculosis) you get what you need. Ann Rheum Dis. 2012;71:1757–60.