

CONSENSUS STATEMENT

Spanish Evidence-Based Guidelines on the Treatment of Moderate to Severe Psoriasis with Biologic Agents

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Abstract. Psoriasis vulgaris is an inflammatory skin disease that is generally chronic and that affects between 1 % and 2 % of the population in industrialized Western countries. It is associated with a marked decline in quality of life. A wide range of treatments are currently available, although surveys conducted before the advent of biologic agents reflected a strong degree of dissatisfaction with the treatments then available. Extensive scientific evidence has been gathered on the safety of biologic agents, and this has led to a review of the role of systemic treatment in general and has allowed new therapeutic goals and strategies to be contemplated in patients with moderate to severe psoriasis. In this new situation, there is a need for Spanish guidelines on the treatment of moderate to severe psoriasis with biologic agents, drafted by consensus among specialists and ratified by the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology (AEDV). These guidelines should be evidence-based with regard to the pharmacologic characteristics, mechanism of action, administration route and regimen, efficacy, contraindications, adverse effects, and cost estimates of biologic agents approved for the treatment of moderate to severe psoriasis in Spain.

Key words: psoriasis, biologic agents, guidelines, treatment, etanercept, adalimumab, infliximab, efalizumab, biologic therapy.

DIRECTRICES ESPAÑOLAS BASADAS EN LA EVIDENCIA PARA EL TRATAMIENTO DE LA PSORIASIS MODERADA A GRAVE CON AGENTES BIOLÓGICOS

Resumen. La psoriasis vulgar es una enfermedad cutánea inflamatoria, de curso habitualmente crónico, que afecta a un 1-2% de la población en los países occidentales industrializados, y produce una reducción marcada de la calidad de vida de los pacientes. Pese a la diversidad de tratamientos disponibles, las encuestas efectuadas antes del advenimiento de los agentes biológicos demuestran un alto grado de insatisfacción con respecto a los tratamientos disponibles. Se ha acumulado abundante evidencia científica con respecto a la eficacia y seguridad de los agentes biológicos, que ha llevado a revisar el papel del tratamiento sistémico en general y ha permitido contemplar nuevos objetivos y estrategias terapéuticas en los pacientes con psoriasis moderada a grave. En este contexto nuevo se hace necesario establecer, de forma consensuada por especialistas expertos y ratificada por los integrantes del Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología (AEDV), unas directrices para el tratamiento de la psoriasis moderada a grave con agentes biológicos, que incluyan información basada en la evidencia científica disponible acerca de las características farmacológicas,

mecanismo de acción, vía y pautas de administración, eficacia, contraindicaciones, efectos adversos y estimaciones del coste de los agentes biológicos aprobados para el tratamiento de la psoriasis moderada a grave en España

Palabras clave: psoriasis, biológicos, directrices, tratamiento, etanercept, adalimumab, infliximab, efalizumab, terapia biológica.

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Introduction

The Spanish Psoriasis Working Group of the Spanish Academy of Dermatology and Venereology has initiated a project to draft and continually update evidence-based guidelines for the systemic treatment of psoriasis with biologic agents. The present consensus statement is a summary of those guidelines, and the tables summarize the pertinent information for each biologic agent.

The aim is to provide dermatologists with a tool to facilitate evidence-based treatment decisions that will contribute to the optimum treatment of patients with moderate to severe psoriasis and also serve as a reference for hospital management and health authorities.

Background

Psoriasis is a chronic recurrent skin disease that affects 1.4% of the Spanish population.¹ Our understanding of psoriasis has been transformed in recent years by the recognition that it is linked to a series of comorbidities with considerable impact on mortality and morbidity in patients with severe forms of the disease. As a result, psoriasis is now considered to be a systemic disease with predominantly cutaneous manifestations,² a significant negative impact on quality of life,³ and physical, emotional, sexual, and financial repercussions. The clinical course of the disease is variable and its natural history poorly understood. While response to intermittent therapy is satisfactory in some patients, a permanent treatment regimen is required in most cases.

Psoriatic arthritis is an often disabling, inflammatory joint disease. Typically, arthritis appears some 10 years after the skin disease is diagnosed; prevalence varies between 6% and 42% depending on the population studied.⁴⁻⁶ Since the cutaneous symptoms precede arthritis in most patients,⁷ it is thought that the cumulative prevalence must be greater. In the first epidemiologic study carried out in Spain, 13% of a population of 3320 patients with moderate to severe psoriasis had a confirmed diagnosis of psoriatic joint disease.⁸

In clinical practice, dermatologists usually define disease severity with either the Psoriasis Area and Severity Index (PASI) or the percentage of affected body surface area (BSA) (assuming the palm of the hand to be equivalent to 1% of the body's surface area).^{9,10} Although essential in clinical trials for the correct assessment of response to treatment, objective assessment of skin involvement alone is, in many cases, an inadequate criteria for defining disease severity from the standpoint of the patient's needs, and consensus has now been reached on an operative definition of moderate to severe psoriasis as that presented

by patients who are candidates for systemic treatment and/or phototherapy.¹¹

While patients with severe psoriasis typically have significant disease with more than 10% affected BSA, some may have a lower percentage of affected BSA but have psoriasis in areas that are difficult to treat topically or are associated with high functional impairment, such as the face, genitals, hands or feet, nails, scalp, or intertriginous areas. Other forms of psoriasis (erythrodermic, pustular, or guttate) usually require systemic therapy (including photochemotherapy). Patients with psoriatic arthritis require systemic treatment (generally methotrexate or tumor necrosis factor [TNF] α inhibitors) irrespective of the percentage of affected BSA. Patients with more limited skin involvement in whom the disease is not adequately controlled by topical therapy and results in physical or mental impairment or disability, should also be considered candidates for systemic therapy and/or phototherapy.

A number of systemic therapies have been approved for the treatment of psoriasis, including phototherapy (ultraviolet radiation: ultraviolet A [UV-A], broadband and narrowband ultraviolet B [UV-B]), photochemotherapy (psoralen plus UV-A [PUVA]), traditional systemic agents (cyclosporine, methotrexate, and acitretin), and biologics (efalizumab, etanercept, infliximab, and adalimumab). These therapies can be used alone, in combination with topical therapies, or in combination with each other (although not all combinations are appropriate). The choice of appropriate therapy should be based on extensive clinical experience on the part of the prescribing dermatologist and on the individual characteristics of the patient and the disease in each case.

Both phototherapy and traditional systemic therapies for psoriasis are associated with the risk of acute and long-term toxicity, including cancer (cyclosporine, photochemotherapy) and teratogenicity (methotrexate and acitretin), and are contraindicated in some subgroups of patients. In some cases, these treatments are expensive or impractical for logistical reasons (availability of phototherapy centers or the loss of work time entailed), and in a significant percentage of patients disease proves to be refractory to treatment.¹² Although the response rate obtained with these therapies at 8 to 16 weeks is in many cases comparable to that of biologics,^{13,14} little is known with respect to long-term response, and clinical experience indicates that sustaining an acceptable response using phototherapy or traditional systemic therapies very often requires the use of doses associated with significant cumulative toxicity. This combination of factors helps to explain why in surveys carried out before biologics were incorporated into routine practice approximately 70% of patients reported being relative unsatisfied or only moderately satisfied with

Table 1. Evidence Levels

1.	The therapeutic intervention is supported by a meta-analysis that includes at least 1 high-quality (eg, including sample-size calculation, flow chart, intention-to-treat analysis, and sufficient size) randomized double-blind study in which the results of the studies are consistent with one another or by a number of high-quality studies with consistent results.
2.	The therapeutic intervention is supported by 1 high-quality study, several studies of lesser quality, or nonrandomized, case-control, or cohort studies with consistent results.
3.	The therapeutic intervention is supported by 1 study of lesser quality or a number of noncomparative studies with consistent results.
4.	Little or no systematic empirical evidence (includes expert opinion)

Adapted from Nast et al²¹.

the treatment prescribed,^{15,16} and nearly 40% reported high levels of noncompliance with treatment.¹⁷

Biologics have a good efficacy-risk profile because they are specifically designed to block target molecules involved in the pathogenesis of psoriasis. This profile has been confirmed by the results of large clinical trials and postmarketing studies in patients with psoriasis and other indications.

The European Medicines Agency (EMA) has approved the biologic agents efalizumab, infliximab, etanercept, and adalimumab for the treatment of moderate to severe plaque psoriasis in adults who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA.

Some expert panels have proposed biologics as first-line therapy for the management of moderate to severe psoriasis.¹⁸ However, because of the high cost of these drugs and the relatively limited experience with their clinical use, evidence-based guidelines and expert consensus statements are needed to maximize the therapeutic benefit to patients and to optimize effective and safe prescription of biologics. Although several national guidelines have been published dealing with the therapeutic management of psoriasis specifically with biologics¹⁸⁻²⁰ or in general,²¹ national guidelines specifically for Spain are needed because of the peculiarities of each health setting, and this need is the motive for the present document.

These guidelines review the available scientific evidence concerning the efficacy and safety of efalizumab, etanercept, infliximab, and adalimumab in the management of moderate to severe psoriasis, the criteria for selecting candidates for treatment with biologics, and therapeutic

strategy with respect to start of treatment, response, treatment failure, maintenance, withdrawal, retreatment, and adjustment of treatment in each case.

Methods

The present guidelines were drawn up by a panel of experts all of whom are members of the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology and specialists with particular experience in the management of moderate to severe psoriasis. Before publication, the document was reviewed by all the members of the working group.

The authors consulted all the guidelines,¹⁸⁻²¹ systematic reviews,²² and meta-analyses²³⁻²⁵ published to date on the subject of the use of biologics in the treatment of psoriasis. The Medline and Cochrane databases were searched for clinical trials with efalizumab, etanercept, infliximab, and adalimumab published between 2000 and 2008, and the published studies obtained in this way were then evaluated according to predefined criteria (Table 1)²¹ to establish the level of evidence and strength of recommendation in each case. Specific bibliographic searches were then carried out to complete the available information.

The present guidelines contain the best information available at the time of writing, and regular updates are planned. The conclusions and recommendations may be modified by new data as these become available. The object of the present guidelines is to provide an aid to the dermatologist in the management of moderate to severe psoriasis with biologic agents, and it is not intended to be a strict treatment guide since all treatment decisions must be taken on a case-by-case basis with the sole object of benefiting the patient. Adherence to these guidelines will not necessarily ensure successful treatment or eliminate the possibility of adverse effects.

Candidates for Treatment with Biologic Agents

In general terms, biologic therapy is indicated (according to the EMA Summaries of Product Characteristics [SPCs]) in the treatment of adult patients 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 PUVA. In most of the clinical trials of biologics undertaken for submission to regulatory agencies in order to obtain marketing authorization, the only criteria for inclusion was moderate to severe psoriasis (a PASI score of 10-12), and therefore the Food and Drug Administration (FDA) does not include the criterion mentioned above.

Moreover, no general definition of moderate to severe psoriasis has been established; in a consensus document published recently in Spain, moderate to severe psoriasis was defined as psoriasis that requires (or has previously required) systemic therapy (including traditional drugs, biologics, and photochemotherapy).²⁶ According to that consensus document, systemic treatment is indicated in cases that fulfill any of the following conditions: disease that is not controlled with topical treatment, extensive affected area (BSA of 5%-10%), a PASI score of 10, rapid worsening, involvement of areas that are visible or associated with functional impairment (palmoplantar or genital), a subjective perception of severity (Dermatology Life Quality Index >10), presence of erythroderma or extensive pustular psoriasis, or psoriasis associated with psoriatic arthritis.

The choice of a biologic agent should be made on a case-by-case basis taking into account factors such as the presence of concomitant disease and psoriatic arthritis, the patient's age and weight, and the risk of possible adverse effects, as well as the past history (including prior treatment) and current characteristics of the disease, and the degree of psoriatic activity at the time of prescription.

For ethical reasons and to ensure equitable treatment, all the biologic agents approved for the treatment of psoriasis must be made available to any patients who are candidates for such treatment, without unnecessary delay or any type of limitation that might imply unequal treatment.

Prescribers of Biologic Treatment for Patients with Psoriasis

Biologic agents should be prescribed by dermatologists with broad experience in the treatment of psoriasis with traditional systemic agents and biologic agents, and the severity of the patient's condition must be objectively documented before, during, and at the end of every course of treatment in order to assess the efficacy of treatment in every patient.

Biologic Agents Approved in Spain for the Treatment of Moderate to Severe Plaque Psoriasis

T-Cell Modulators

Efalizumab

Efalizumab (Raptiva, MerckSerono) is a recombinant humanized monoclonal antibody (immunoglobulin [Ig] G1κ) produced in genetically engineered Chinese hamster ovary (CHO) cells that binds specifically to CD11a, the α subunit of lymphocyte function-associated antigen-1

(LFA-1), an adhesion molecule in leukocytes that plays an important role in T-cell activation and traffic. In binding to CD11a, efalizumab blocks the interaction between LFA-1 and intercellular adhesion molecule 1, thereby inhibiting T-cell activation and interfering with the binding of T cells to endothelial cells and, consequently, with T-cell traffic. Administration of efalizumab reduces CD11a expression in T cells (expression returns to normal 7 to 10 days after elimination of the drug) and produces a reversible increase in the number of circulating lymphocytes, probably by inhibiting their extravasation. Approximate bioavailability of efalizumab following subcutaneous administration is 50%, and serum concentrations reach a steady state after the fourth dose. The mean (SD) half-life of efalizumab at a dose of 1 mg/kg is 6.21 (3.11) days.²⁷

The only EMEA approved indication is "treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA."

Efalizumab, which is supplied as a lyophilized powder (150 mg/vial) that must be reconstituted with water, is administered subcutaneously once a week by the patient or a third party. An initial single dose of 0.7 mg/kg body weight is given, followed by the standard dose of 1 mg/kg.

To date, the efficacy and safety of efalizumab have been evaluated in over 3500 patients with moderate to severe plaque psoriasis in various clinical trials in all research phases. The duration of the phase III trials ranged from 12 weeks to 3 years of continuous treatment. In the postmarketing phase, it is estimated that worldwide the cumulative exposure to efalizumab in May 2007 included over 40 000 patients and was equivalent to approximately 28 000 patient-years.²⁸

Efficacy: Clinical Trials with Efalizumab

1. *Short-term results (12 weeks)*. Clinical trials in patients with moderate to severe plaque psoriasis (PASI >12) have shown greater efficacy with efalizumab than with placebo after 12 weeks of treatment.²⁹⁻³⁴ In these clinical trials, the results of which are summarized in Table 2, the percentage of patients who achieved an improvement in PASI from baseline of at least 75% (a PASI 75 response) after 12 weeks of treatment with efalizumab at a dose of 1 mg/kg/wk ranged from 22%²⁹ to 38.9%.³²

The Clinical Experience Acquired with Raptiva (CLEAR) trial, a study that enrolled 793 patients, included a cohort of 526 patients defined prospectively as "high need" cases. These patients had a contraindication to or a history of treatment failure with at least 2 systemic treatments (the conditions stipulated by the EMEA Summary of Product Characteristics [SPC]).

Table 2. Summary of Clinical Trials with Efalizumab 1 mg/kg

Reference	Baseline Characteristics				PASI 75 Patients (%)	
	Drug		Placebo		Drug	Placebo
	No (% Male)	PASI: Mean (SD) or Mean (Range)	No (% Male)	PASI: Mean (SD) or Mean (Range)		
Lebwohl et al 2003 ²⁹	232 (65%)	20.0 (no data)	122 (65%)	20.0 (no data)		
Gordon et al 2003 ³⁰ Menter et al 2005 ³¹	369 (68%)	19.4 (10.1-58.7)	187 (71%)	19.4 (11.4-50.3)	98 (26.6%)	8 (4.3%)
Leonardi et al 2005 ³²	162 (72.8%)	18.6 (11.9-50.1)	170 (72.9%)	19.0 (9.6-57.6)	63 (38.9%)	4 (2.4%)
Papp et al 2006 ³³	50 (67.3%)	191 (7.5)	236 (59.3%)	18.7 (7.0)	106 (23.6%)	7 (3.0%)
Dubertret et al 2006 ³⁴	529 (67.3%)	23.6 (9.7)	264 (67.4%)	23.0 (9.6)	166 (31.4%)	11 (4.2%)

Abbreviation: PASI, Psoriasis Area and Severity Index.

In this high-need group, PASI 75 response rates at week 12 were 29.5% for the patients receiving efalizumab (compared to 2.7% for the placebo group). These rates are similar to those of the full study population in this trial (31.4% for efalizumab versus 4.2% for placebo).³⁴ The meta-analyses carried out indicate that the relative risk compared to placebo of achieving a PASI 75 at week 12 in patients receiving efalizumab 1 mg/kg/wk was 7.34 (95% confidence interval [CI], 5.23-10.30),²⁴ the risk difference with respect to placebo was 0.24 (95% CI, 0.19-0.30),²⁵ and the number needed to treat to achieve a PASI 75 was 4 (95% CI, 3.36-5.24).²⁴

2. *Results after 24 weeks.* Sustained clinical improvement was observed in the trials in which treatment with efalizumab was prolonged after 12 weeks. Continued improvement was observed in a 12-week placebo-controlled trial in which patients were given the opportunity to continue with open-label therapy with efalizumab for a further 12 weeks, after which 43.8% of the patients had a PASI 75.³¹

In another study, patients who had not achieved a PASI 75 after 12 weeks of treatment were once again randomized to receive treatment with efalizumab 1 mg/kg/wk or placebo for a further 12 weeks.³² After 24 weeks of treatment, 20.3% of these ("slow response") patients achieved a PASI 75 compared to 6.7% of the placebo group.

In the subgroup of patients in the CLEAR trial whose response at week 12 was better than PASI 50 but less than PASI 75, 47.5% achieved a PASI 75 response following the open-label prolongation of treatment for a further 12 weeks.³⁵ Of the patients in that trial who started out with placebo and then switched to efalizumab after week 12, 24.1% achieved a PASI 75 response.

3. *Relapse and retreatment.* Mean time to relapse (defined as the loss of 50% of the improvement achieved in the PASI score) after discontinuation of treatment in patients who had achieved a PASI 75 varied from 54³⁵ to 84 days.²⁹ Retreatment produced a mean improvement of 62.3% with respect to the baseline values determined at the start of the study.³⁵

4. *Results of long-term continuous treatment (3 years).* An open-label study of continuous treatment that was extended to 36 months provides data on continuous treatment with efalizumab.³⁶⁻³⁸ During the initial 12 weeks (first phase), 339 patients received a weekly subcutaneous dose of efalizumab 2 mg/kg; by the end of this initial treatment period, 41.3% of the patients had achieved a PASI 75 and 13.0% a PASI 90. After 12 weeks, only the patients who achieved at least a 50% improvement in PASI or a static Physician's Global Assessment (PGA) category of mild, minimal, or clear were eligible to remain in the study during the second phase and received maintenance therapy with a weekly subcutaneous dose of efalizumab 1 mg/kg. During the first 15 months of treatment, patients could receive up to the maximum dose of 4 mg/kg temporarily. Intention-to-treat analyses of response demonstrated sustained treatment efficacy with efalizumab throughout the whole study. The percentages of patients who obtained PASI 75 and PASI 90 responses after 36 months of treatment were 45.4% and 24.5%, respectively.³⁸

Special Considerations

1. *Obese patients.* Efalizumab is considered to be particularly appropriate in the treatment of overweight patients because the dose can be adjusted to take this circumstance into account without loss of treatment efficacy.^{39,40}

2. *Palmoplantar psoriasis*. Open-label studies and anecdotal observations have been published that suggest that treatment with efalizumab could be effective in some patients with palmoplantar psoriasis.^{41,42}

Safety

Efalizumab is contraindicated in patients known to be hypersensitive to the drug or any of the excipients. Before prescribing treatment with efalizumab, the physician should rule out the presence of active tuberculosis or other serious infections, immunodeficiency, or any history of malignancy. Treatment with efalizumab is not recommended in women who are pregnant (FDA category C) or breast-feeding.⁴³

Efalizumab is generally well tolerated, although flu-like symptoms, such as headache, nausea, chills, and muscle aches are common in the days just after the injection, especially at the start of treatment (27.4% versus 21.2% in the placebo group); the incidence of this side effect declines significantly after the third injection (3.7% compared to 3.9%).³³ A lower initial dose (0.7 mg/kg) is used to minimize the incidence of this adverse effect. These symptoms typically respond to treatment with paracetamol.

A large meta-analysis of the clinical trials carried out indicated that the incidence of malignancies observed during treatment with efalizumab (including lymphoproliferative disease, solid tumors, melanoma, and nonmelanoma skin cancer) was similar to that of the controls and was the expected rate for this population of patients.⁴⁴ In the overall analysis of the results of a number of clinical trials at week 12, the overall incidence of infections in patients receiving efalizumab was 28.6% compared to 26.3% in those receiving placebo.^{45,46} Nor were significant differences found in more long term studies.²⁷ Isolated cases have been reported of serious infections (cellulitis, pneumonia, sepsis, opportunist infections, and 2 cases of progressive multifocal leukoencephalopathy) since the drug has been marketed.⁴⁷

As reactivation of latent tuberculosis has not been reported, it is not necessary to start chemoprophylaxis before initiating treatment with efalizumab. However, most experts do recommend ruling out the presence of inactive tuberculosis before starting any biologic treatment.⁴⁸

During treatment, between 40% and 50% of patients present sustained elevation of leukocyte and lymphocyte counts (2.5-3.5 times the upper limit of normal). This abnormality, which is related to the mechanism of action of the drug, resolves when treatment is discontinued. While continuous monitoring of laboratory parameters is not considered necessary, monthly blood cell counts should be obtained during the first 3 months of therapy and quarterly thereafter because thrombocytopenia has been reported in a small percentage (0.3%) of patients

in clinical trials. Elevated alkaline phosphatase and alanine aminotransferase levels have also been reported in a small percentage of patients (approximately 5%).⁴³ There have been occasional reports of hemolytic anemia and pancytopenia and rare cases of inflammatory polyradiculopathy and peripheral demyelination.²⁰ No organ-specific toxicity or drug interactions have been reported, and for this reason dose does not have to be adjusted to take into account the patient's regular medication.⁴³

Some patients present psoriasis-related side effects, including exacerbations in the form of localized papular eruptions or changes in morphology (for example the development of small plaques of inverse or guttate psoriasis). In clinical trials, this type of adverse event has been reported in 2.2% of patients receiving efalizumab compared to 0.8% of the controls. Another such effect is worsening of psoriatic arthritis (1.6% as compared to 1.3% in controls).⁴⁶ Transient flares normally respond to concomitant therapy with treatments such as topical corticosteroids, narrowband UV-B light therapy, or short courses of systemic treatment if tolerated by the patient.⁴⁹⁻⁵¹

Clinical Management

Efalizumab is designed for use as a long-term continuous treatment in patients who show a satisfactory response. Treatment may, however, have to be withdrawn for a number of reasons including adverse events, insufficient response, infections, surgical procedures, pregnancy, or personal circumstances. As occurs with other antipsoriasis therapies, a slow general relapse approximately 3 months after withdrawal is to be expected, and the response to retreatment is similar to that obtained in patients treated for the first time.⁵² Of particular clinical significance is the possibility of a rebound effect (a deterioration of the psoriasis equivalent to at least 125% of the baseline PASI) in some cases associated with a morphological change (small plaques, pustular, or erythrodermic psoriasis). Rebound usually occurs when treatment is discontinued, and it is observed in 14.6% of patients who present an unsatisfactory response (PASI < 50), 9.5% of patients in the placebo group, and 5.7% of those who show a satisfactory response to treatment.⁵³

There is no evidence from clinical trials supporting any particular strategy for dealing with a generalized inflammatory exacerbation. However, according to dermatologists specialized in treatment with efalizumab, a course of 3 to 6 weeks of methotrexate, cyclosporine, or phototherapy at standard doses should be added to the treatment regimen to control the exacerbation and to facilitate the continuation of treatment with efalizumab.^{49-52,54} When efalizumab treatment does not produce

a satisfactory response or has to be discontinued for any reason, an appropriate strategy for managing the transition may be to overlap treatment for a few weeks with another effective and fast-acting systemic therapy in order to prevent a possible rebound effect, particularly in patients considered to be nonresponders.

Since efalizumab does not improve joint symptoms in patients with psoriatic arthritis, it is not a first-line treatment in this subgroup. The joint pain and arthritis reported during treatment with efalizumab and even after withdrawal of such treatment may be a manifestation of new onset joint involvement or alternatively may be an aggravation or early sign of pre-existing psoriatic arthritis. Some patients who are satisfied with the improvement in their skin lesions may prefer to continue with efalizumab despite the joint symptoms.⁵³ In some patients in whom treatment with efalizumab was discontinued because of arthritis, it has been restarted successfully without any reappearance of rheumatologic symptoms.⁵³ In a retrospective analysis of 16 patients who developed de novo arthritis during treatment with efalizumab, reintroduction of the drug was followed by recurrence of rheumatologic signs and symptoms in 2 patients.⁵⁵ All 16 of those patients fulfilled the criteria for psoriatic arthritis. However, although efalizumab was ineffective in treating psoriatic arthritis in a phase II randomized double-blind placebo-controlled study undertaken to evaluate its usefulness in these patients, no worsening of the symptoms was observed.⁵⁶

When joint symptoms develop during treatment with efalizumab, the recommended strategy is to start symptomatic treatment with nonsteroidal anti-inflammatory drugs and to continue with the course of efalizumab while establishing a differential diagnosis for other kinds of joint disease. It may occasionally be necessary to switch the patient to another systemic therapy (for example, an anti-TNF agent), particularly when treatment with efalizumab ceases to be effective or there is a rebound of psoriasis.

Cost

The cost of the drug required to treat an average patient weighing 75 kg with efalizumab for 24 weeks is €5760 (price to retailer on www.portalfarma.com).

Table 3 summarizes the information and recommendations for efalizumab.

Tumor Necrosis Factor α Inhibitors

The response of the disease to treatment with anti-TNF biologics is the primary confirmation of the role of this cytokine in the pathogenesis of psoriasis. There

are currently 3 biologic agents approved by the EMEA for the treatment (second line) of adults with moderate to severe psoriasis: 1 fusion protein (etanercept), 1 chimeric monoclonal antibody (infliximab), and 1 human monoclonal antibody (adalimumab). Infliximab is approved for the treatment of active and progressive psoriatic arthritis either in combination with methotrexate or as monotherapy in patients who are intolerant to methotrexate or have contraindications to this drug. Etanercept and adalimumab are approved as monotherapy for this indication.

Given their efficacy in the treatment of psoriatic arthritis, these drugs are particularly indicated in patients with moderate to severe psoriasis associated with psoriatic arthritis. There appear to be no significant differences between the different TNF inhibitors with respect to their effect on psoriatic arthritis.⁵⁷

Since many of the potential adverse effects associated with the mechanism of action of TNF inhibitors are class effects, the safety considerations are similar in many cases (although they are described separately for each drug in the present document). From the dermatological standpoint, an important consideration is the paradoxical effect that has recently been recognized in patients with psoriasis treated with TNF antagonists. In some cases treatment with these biologics can cause exacerbation of skin lesions⁵⁸ or onset of guttate psoriasis⁵⁹ or plantar pustulosis.^{58,59} These adverse events had already been reported among rheumatology patients and in relation to other indications for TNF antagonists. This paradoxical reaction—which can lead to withdrawal of treatment—is sometimes (although not always) specifically related to a particular drug, in which case an alternative TNF inhibitor can be used.⁵⁹

Fusion Protein

Etanercept

Etanercept (Enbrel, Wyeth) is a dimeric protein of human origin genetically engineered by fusing the soluble extracellular domain of TNF receptor-2 (RTNF2/P75) to the Fc domain of human IgG1. It is produced by recombinant DNA technology in a system of CHO cells. Unlike infliximab and adalimumab, etanercept binds not only to TNF- α but also to lymphotoxin- α (TNF- β). It is thought that etanercept binding is restricted to the trimer forms of soluble and transmembrane TNF and that it does not bind to the monomer and dimer forms. It is also believed that it does not activate the complement and probably does not produce antibody-dependent cell-mediated cytotoxicity.⁶⁰ When etanercept is administered by subcutaneous injection it has a bioavailability of 76% and a half-life of approximately 70 hours after a single

Table 3. Efalizumab: Summary and Recommendations

1. Indication (EMA): treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA
2. Date of approval: EMA 09/22/2004, FDA 10/27/2003
3. Dose regimens: 0.7 mg/kg first dose followed by 1 mg/kg/wk given subcutaneously
4. Clinical response: expected within 4-8 weeks, making it inadvisable to use this drug when rapid control of the disease is required
5. Short-term efficacy: 22%-39% of patients achieved a PASI 75 at 3 months (evidence level 1)
6. Medium-term efficacy: 44% of patients achieved a PASI 75 at 6 months (evidence level 2)
7. Long-term treatment: prolonged remission in a subgroup of patients with good response; 45% of patients achieved a PASI 75 at 3 years (evidence level 3)
8. Contraindications: hypersensitivity to efalizumab, malignant tumors, tuberculosis or other serious infections, and immunodeficiency Do not administer live vaccines
9. Adverse reactions: flu-like symptoms are common at the start of treatment. Elevated leukocyte and lymphocyte counts are common. The following adverse effects have also been reported: thrombocytopenia, hemolytic anemia, pancytopenia, polyradiculopathy, peripheral demyelination, and serious infections including cellulitis and pneumonia.
10. Baseline monitoring: standard laboratory workup, tuberculin skin test, hepatitis and HIV serology
11. Ongoing monitoring during treatment: complete blood counts monthly for the first 3 months and at periodic intervals thereafter; standard laboratory workup and regular clinical follow-up
12. FDA pregnancy category: C
13. Other issues and recommendations: Some patients may develop exacerbations or changes in morphology, and may experience rebounds of the psoriasis. Avoid abrupt withdrawal of treatment. Efalizumab is not effective in psoriatic arthritis. Aggravation and development of joint pain and new-onset psoriatic arthritis have been reported. Weight-adjusted dosing is used, and the drug is equally effective in obese patients. Response to efalizumab should be assessed at 12 weeks. If an improvement in PASI of at least 50% from baseline has not been achieved by that time, a switch to an alternative treatment should be considered. However, this decision may be postponed for several weeks at the discretion of the clinician since time to onset of therapeutic effect is not the chief consideration when efalizumab is the treatment of choice or when it is replaced by an alternative therapy. Rebounds are common and occur more often in patients with a poor response to treatment. These patients are more susceptible to the rebound effect and should be treated with the drug that has the highest expected rate of response and the shortest time to response. Although retreatment is generally associated with a good response, patients should be warned against discontinuing treatment without consultation because of the risk of rapid relapse or rebound. It is often advisable to use a systemic treatment as a transition strategy when efalizumab is temporarily withdrawn or replaced by another agent, overlapping the 2 regimens until the expected onset of the therapeutic effect of the new drug. Efalizumab may be the first-line treatment of choice in patients with latent tuberculosis infection when chemoprophylaxis is not considered advisable and in patients particularly at risk for developing the adverse effects associated with TNF inhibitors (heart failure, demyelinating disease, lupus erythematosus, etc). Patients should be warned about the risk of increased susceptibility to infection, and the appropriate diagnostic tests and early treatment should be carried out. In cases of serious infection (or major surgery with risk of infection) treatment with efalizumab should be temporarily suspended.

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; PASI, Psoriasis Area and Severity Index; PUVA, psoralen plus ultraviolet A radiation; TNF, tumor necrosis factor. ultravioleta A; TNF: factor de necrosis tumoral; VIH: virus de la inmunodeficiencia humana.

administration and 100 hours during maintenance treatment.⁶¹

Etanercept is approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, and the “treatment of adults with moderate to severe plaque psoriasis who

failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA.”⁶²

It is supplied in the form of prefilled 25 or 50 mg syringes and vials containing 25 mg of lyophilized powder in 4-pack cartons. The recommended dose for the

treatment of psoriasis is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice-weekly may be administered for up to 12 weeks followed, if necessary, by either 25 mg twice weekly or 50 mg once weekly. Treatment with etanercept should continue until remission is achieved or for a maximum of 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If retreatment with etanercept is indicated, the above recommendations on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

Efficacy: Clinical Trials with Etanercept

1. *Short-term results (up to 24 weeks).* The following 6 clinical trials were evaluated in this analysis: 3 that evaluated the efficacy of etanercept after 24 weeks of treatment with different dose regimens,⁶³⁻⁶⁵ 1 that studied a dose of 50 mg once weekly,⁶⁶ a 24-week study that compared continuous treatment with 12 weeks of intermittent treatment,⁶⁷ and a clinical trial of retreatment that assessed the results of withdrawal and a second course of treatment.⁶⁸ An integrated analysis of the first 3 clinical trials is also discussed.⁶⁷

In the first 3 clinical trials in patients with moderate to severe plaque psoriasis (PASI=10), subcutaneous administration by the patient or physician of etanercept 25 mg twice weekly produced a PASI 75 response in between 30% and 34% of patients at week 12 and between 44% and 56% at week 24.⁶³⁻⁶⁵ The corresponding percentages for a dose of 50 mg twice weekly were 49% at week 12 and 59% at week 24. In the most recently published study, administration of 50 mg twice weekly for 12 weeks before continuing with 25 mg twice weekly for a further 12 weeks increased the PASI 75 rate to 49% at week 12 and 54% at week 24.⁶⁵ With this dose regimen, 97% of the patients who achieved a PASI 75 at week 12 maintained this response at week 24, and almost one-third of the patients who did not achieve a PASI 75 at week 12 had achieved it by week 24 despite the reduction in the dose. This regimen, which accelerates the onset of response and maximizes its duration while reducing the overall cost of treatment, is the one generally used in current practice, although the results of some studies confirm the efficacy and safety of long-term maintenance treatment.

The data from these 3 clinical trials were combined to provide an integrated analysis of a population of 1187 patients who had received placebo, etanercept 25 mg twice weekly, or etanercept 50 mg twice weekly for more than 12 weeks.⁶⁹ The integrated analysis showed that the PASI 75 response was dose-dependent and

revealed a statistically significant difference between the 2 treatment regimens and the placebo group from week 4 onwards ($P < .05$). However, at the beginning of the study a substantially higher percentage of patients achieved a PASI 75 response in the 50 mg twice weekly group than in the 25 mg twice weekly group. At week 12, a significantly larger percentage of the patients in both the etanercept 25 mg twice weekly group (33%) and the etanercept 50 mg twice weekly group (49%) achieved a PASI 75 response compared to the placebo group (3%; $P < .05$). A trial was carried out in 9 European countries to assess the efficacy and safety of etanercept 50 mg once weekly for 24 weeks.⁶⁶ The study design included 2 phases: in the first phase patients were randomized to receive placebo (n=46) or etanercept 50 mg (n=96) once weekly for 12 weeks; in the second 12-week phase all the patients received etanercept 50 mg once weekly. At week 12, 37.5% of the patients receiving etanercept had achieved an improvement of 75% in PASI score as compared to 2.2% of the patients receiving placebo. At week 24, 71.1% and 11.1% of the patients in the etanercept/etanercept group achieved PASI 75 and PASI 100, respectively, compared to 44.4% and 5.6% respectively in the placebo/etanercept group.⁶⁶

The characteristics of these trials are summarized in Table 4.

The meta-analyses carried out indicate that the relative risk with respect to placebo of achieving a PASI 75 at week 12 in patients receiving etanercept 25 mg twice weekly was 10.20 (95% CI, 5.87-17.72),²⁴ the risk difference with respect to placebo was 0.30 (95% CI, 0.25-0.35),²⁵ and the number needed to treat to achieve a PASI 75 response was 4 (95% CI, 2.96-4.10).²⁴ At week 12, the relative risk of achieving a PASI 75 response in patients receiving etanercept 50 mg twice weekly was 11.73 (95% CI, 8.04-17.11),²⁴ the risk difference with respect to placebo was 0.44 (95% CI, 0.40-0.48),²⁵ and the number needed to treat to achieve a PASI 75 response was 3 (95% CI, 2.07-2.49).²⁴

1a. *Continuous or intermittent (with interruptions) treatment.* In an open-label randomized trial, the efficacy and safety of 24 weeks of continuous treatment with etanercept was compared to 12 weeks of intermittent treatment.⁶⁷ During the first 12 weeks, all the patients received uninterrupted treatment with etanercept 50 mg twice weekly. This was followed by a further 12 weeks of either continuous treatment with etanercept 50 mg once weekly (n=1272) or intermittent treatment (n=1274) with etanercept 50 mg once weekly depending on response measured using the PGA. The primary outcome measure was the proportion of patients who showed a response

Table 4. Etanercept: Summary of Main Clinical Trials (Results at week 12)

Reference	Baseline Characteristics				PASI 75 Patients (%)	
	Drug		Placebo		Drug	Placebo
	No (% Male)	PASI, mean (SD)	No (% Male)	PASI, Mean (SD)		
Gottlieb et al 2003, ⁶³ 25 mg twice weekly	57 (58%)	17.8 (1.1)	55 (67%)	19.5 (1.3)	17 (30%)	1 (2%)
Leonardi et al 2003, ⁶⁴ 50 mg twice weekly	164 (65%)	18.4 (0.7)	166 (63%)	18.3 (0.6)	81 (49%)	6 (4%)
Leonardi et al 2003, ⁶⁴ 25 mg twice weekly	162 (67%)	18.5 (0.7)	166 (63%)	18.3 (0.6)	55 (34%)	6 (4%)
Papp et al 2005, ⁶⁵ 50 mg twice weekly	194 (67%)	19.5 (8.8)	193 (64%)	18.6 (8.6)	96 (49%)	6 (3%)
Papp et al 2005, ⁶⁵ 25 mg twice weekly	196 (65%)	19.1 (8.2)	193 (64%)	18.6 (8.6)	67 (34%)	6 (3%)
Vandekerkhof et al 2008 ⁶⁶ 50 mg once weekly	96 (61.5%)	21.4 (9.3)	46 (54.4%)	21.0 (8.6)	36 (37.5%)	1 (2.2%)

Abbreviation: PASI, Psoriasis Area and Severity Index.

at week 24 (those who achieved a PGA score ≤ 2 and improvement from baseline). At week 12, the authors observed comparable high percentages of patients with response in both the group assigned to continuous treatment (71.3%) and the group assigned to intermittent treatment (72.0%). However, during the second 12-week phase a higher percentage of patients achieved a response in the group receiving continuous treatment throughout the whole 24-week period than in the group who received intermittent treatment during the second phase (71.0% compared to 59.5%; $P < .0001$).⁶⁷ This study reinforces the use of the treatment regimen specified by the SPC, which states that treatment with etanercept should be continuous for 24 weeks.

1b. *Relapse and retreatment.* In an extension of the 24-week study by Leonardi et al,⁶⁴ it was observed that following withdrawal of therapy patients tended to experience relapse after a median of approximately 3 months, but did not experience rebound or develop more severe forms of the disease (pustular or erythrodermic psoriasis).⁶⁸ A second course of treatment with etanercept achieved satisfactory control of the disease, and retreatment was not associated with the formation of neutralizing antibodies or any increase in injection site reactions. The percentages of patients who achieved a PASI 75 during the second course of treatment were similar to those who achieved

this response with the first course: 49% and 58% after 24 weeks of retreatment with etanercept 25 mg and 50 mg twice weekly, respectively.⁶⁸

2. *Long-term treatment (more than 24 weeks).* The long-term efficacy of continuous treatment with etanercept for more than 24 weeks in the management of moderate to severe plaque psoriasis has been evaluated in 2 studies, 1 denominated with company code 117 (132 weeks)⁷⁰ and 1 with company code 115 (2.5 years).⁷¹

The first of these was a double-blind multicenter clinical trial in the USA and Canada that evaluated the safety and efficacy of high doses of etanercept. The study was divided into 3 phases: in the first phase the patients were randomized to receive either placebo ($n=307$) or etanercept 50 mg twice weekly ($n=311$) for 12 weeks. During the second phase, all the patients were treated with etanercept 50 mg twice weekly for 84 weeks ($n=591$).⁷⁰ In the third phase, in which only the patients located in the USA continued ($n=201$), patients received 50 mg once weekly with the possibility of increasing the dose to 50 mg twice weekly at week 120 or 132 under certain conditions defined in the protocol. Tying et al,⁷⁰ who published the results of the study through week 96, reported a marked reduction in disease severity in terms of PASI 50, 75, and 90 in both the group that received placebo in the first phase followed by etanercept (79.1%, 51.6%, and 22.8%, respectively)

and in the group treated with etanercept throughout (82.6%, 51.1%, and 23.2%).

2a. *Continuous or intermittent (with interruptions) treatment.* Elewski et al⁷¹ reported on the results obtained with the patients from 2 studies^{64,65} who took part in an extension study with a total duration of 2.5 years. Patients received etanercept 50 mg once weekly for 12 weeks with the possibility of doubling this dose if they fulfilled the predefined criteria specified in the study protocol. In this extension study, 912 patients were analyzed in 2 groups: those who had interrupted treatment for 30 days or less (a median of 5 days), and those who had interrupted treatment for more than 30 days. Both groups showed sustained improvement in PASI and PGA scores after 72 weeks of treatment. In the group receiving etanercept 50 mg once weekly, 61% of the patients achieved a PASI 75 at week 12 of the extension and 60% at week 72. In the group of patients who required an increase to a dose of 50 mg twice weekly, 33% achieved a PASI 75 at week 12, and 43% at week 72.⁷¹

In a recently published open-label study, 720 patients were assigned randomly to 1 of 2 treatment groups (continuous or intermittent treatment) for 54 weeks.⁷² Patients in the continuous treatment group received etanercept 25 mg twice weekly. In the intermittent treatment group, patients received etanercept 50 mg twice-weekly for up to 12 weeks or until they achieved a PGA score of at least 2 (mild, minimal, or almost clear); then when relapse (defined as PGA of 3) occurred, treatment was restarted with etanercept 25 mg twice weekly until a PGA of 2 was once again achieved. Mean PGA during the 54 weeks of the study was significantly lower in the patients treated continuously than in the group of patients treated intermittently (1.98 compared to 2.51, $P<.001$). At week 54, there was a significant ($P<.01$) reduction in PGA with respect to the mean baseline score of 3.6 in both the continuous and the intermittent treatment group (1.9 and 2.4, respectively). Mean PASI also decreased significantly from baseline through week 54 in both the continuous (from 21.9 to 7.1) and the intermittent (from 22.8 to 9.5) treatment groups ($P<.01$, within-group comparison). That study showed that satisfactory response can be achieved with approximately 1 year of therapy with both these treatment regimens, although the response achieved with continuous treatment was better.⁷²

Special Considerations

1. *Obesity.* The results of the clinical trials undertaken to date suggest that obese patients may have a suboptimal response to treatment with etanercept at fixed doses.⁴⁰

2. *Psoriatic arthritis.* The efficacy of etanercept in the management of psoriatic arthritis has been demonstrated in several long-term and short-term studies,⁷³⁻⁷⁸ and long-term treatment has been shown to slow the rate of progression of joint damage.⁷⁶ In a multicenter phase III placebo-controlled randomized trial in which 205 patients received placebo (n=104) or etanercept 25 mg twice weekly (n=101) for 24 weeks, 59% and 15% of the patients in the etanercept and placebo groups respectively met American College of Rheumatology preliminary criteria for improvement (ACR 20) ($P<.0001$) at week 12, and these results were maintained at weeks 24 and 48.⁷⁵
3. *Pediatric psoriasis.* In a study that compared treatment with etanercept 0.8 mg/kg/wk (to a maximum of 50 mg) with placebo in 211 children and adolescents (4-17 years of age) with plaque psoriasis, 57% of the patients receiving etanercept achieved a PASI 75 at week 12 compared to 11% of those receiving placebo ($P<.001$).⁷⁷
4. *Combination therapy.* The results of several open-label studies support the efficacy of combination therapy with etanercept in patients with special therapeutic needs. In a randomized pilot study of patients who did not respond adequately to monotherapy with methotrexate (PASI=8 or BSA>10%), a treatment regimen of methotrexate in combination first with etanercept 50 mg twice weekly for 12 weeks and then with 25 mg twice weekly for a further 12 weeks produced complete or almost complete clearance in two-thirds of 31 patients, as compared to one-third of 28 patients in whom treatment with methotrexate was tapered over 4 weeks.⁷⁸ In an open-label case series evaluated retrospectively, the combination of etanercept with methotrexate appeared to improve the response to etanercept in some patients without impairing the safety of the treatment.⁷⁹ At week 12 in an open-label study of 86 patients treated with etanercept 50 mg twice weekly and narrowband UV-B 3 times weekly, 26.0% achieved complete clearance, 58.1% a PASI 90, and 84.9% a PASI 75.⁸⁰

Safety

Etanercept is contraindicated in patients known to be hypersensitive to the drug or any of the excipients. Before prescribing treatment with etanercept, the physician should rule out the presence of active tuberculosis, sepsis or any other serious infection, immunodeficiency, history of malignancy, heart failure (New York Heart Association [NYHA] functional class III-IV), and demyelinating disease. Before, during, and after treatment with etanercept, all patients should be assessed for the presence of infection bearing in mind that the mean elimination half-life of etanercept is approximately 3.5 to 5 days.

Any infection found should be treated appropriately. If inactive (latent) tuberculosis is diagnosed, antituberculosis prophylactic therapy must be started before initiating treatment with etanercept and in accordance with local recommendations. Treatment with infliximab is not recommended in pregnant women (FDA category B) or during breastfeeding.

Skin reactions at the injection site occurred in up to 37% of patients treated with etanercept. Typically, these reactions are mild to moderate and do not require withdrawal of treatment. These reactions usually last between 3 and 5 days and occur during the first month of treatment; incidence tends to decrease thereafter.²⁰ As the needle cover of the prefilled syringe contains latex, this presentation should be avoided in latex allergic patients.

All the clinical trials undertaken with etanercept have analyzed the safety of the drug. With respect to short term therapy, a study of the data from 1347 patients who participated in 3 randomized double-blind clinical trials comparing etanercept with placebo⁸¹ constitutes the largest database of patients with psoriasis treated with etanercept, representing an overall exposure to etanercept of 933 patient-years. Using the data from the first 12 weeks, safety was analyzed in terms of percentage of patients with adverse events, serious adverse events, infections, serious infections, and injection site reactions, and routine laboratory assessments. Altogether, 471 patients (51%) reported at least 1 adverse event: 46% in the group receiving 50 mg twice weekly, 56% in the group receiving 50 mg once weekly, 48% in the group receiving 25 mg once weekly, and 51% in the placebo group. Overall, the occurrence of adverse events was not dose-dependent. With the exception of injection site reactions, adverse event rates for etanercept were similar to those for placebo. The most commonly reported adverse events were headache and ecchymosis at the injection site. Arthritis was less common in patients receiving etanercept (1.2%) than in those who received placebo (3.1%). Serious adverse events were reported by 1% of the patients receiving placebo and by 1.2% of those receiving etanercept; no dose-related differences were observed in the treatment groups. The most common events were infection in the upper airway, sinusitis, and flu-like syndrome, and no differences were observed in this respect between the different treatment groups and the placebo group. Serious infections developed in 0.4% of the patients receiving etanercept and in 1% of those receiving placebo. No patients developed opportunist infections or tuberculosis during the first 12 weeks of the 3 clinical trials included in this analysis. No toxicities related to abnormalities in laboratory test results were reported, and no patients were withdrawn from the study because of such toxicity. The data in this meta-analysis

of 12-week trials comparing different doses of etanercept with placebo reveal a treatment with, in the short term, a favorable risk-benefit profile in patients with moderate to severe plaque psoriasis.⁸¹

With respect to long-term treatment, we analyzed an article concerning the safety of 96 weeks of etanercept treatment at a dose of 50 mg twice weekly.⁷⁰ Total exposure to etanercept 50 mg for the first 96 weeks was 908.9 patient-years. Exposure-adjusted rates of noninfectious and infectious adverse events were similar for the etanercept/etanercept group at weeks 12 and 96, indicating that extended exposure to etanercept did not increase its toxicity. Although the observed incidence of squamous cell carcinoma in this study was higher than would be expected for the general population of the Minnesota-based registry, patients with psoriasis are at increased risk for squamous cell carcinoma.⁷⁰ The degree of risk correlates with the severity of psoriasis, and can be further increased by exposure to phototherapy. In patients with rheumatoid arthritis, the use of etanercept for up to 5 years did not appear to be associated with an increased incidence of squamous cell carcinoma. No demyelination, tuberculosis, or opportunist infections were reported. Assays revealed antibodies to etanercept at least once during the study in 18.3% of patients. All of the anti-*etanercept* antibodies detected were found to be nonneutralizing and had no apparent effect on the efficacy and safety profiles of the drug. A considerable body of long-term data is available in patients with rheumatoid arthritis refractory to disease-modifying antirheumatic drugs who have been treated with etanercept, some for as long as 8.2 years. The safety analyses of a total of 3139 patient-years of exposure to etanercept (mostly at a dosage of 25 mg twice weekly) have not identified any new safety concerns with long-term use of etanercept.⁷⁰

Furthermore, etanercept is also indicated in other diseases (rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, and ankylosing spondylitis) and there has been some 15 years of overall experience in clinical trials and an overall exposure to etanercept of 153 057 patient-years.⁸²

Clinical Management

Etanercept is indicated in the induction therapy of moderate to severe psoriasis. According to the EMEA SPC etanercept is indicated for cyclical treatment and only very rarely gives rise to a rebound effect. Moreover, there is no noticeable loss of response with retreatment.⁶⁸

In long term treatment, a reduction in efficacy may be observed in some patients when the dosage of etanercept is reduced from 50 mg twice weekly to 50 mg once weekly; this effect has also been observed with other TNF

inhibitors.²⁰ Combination treatment (for example with methotrexate) can be effective in increasing the efficacy of etanercept in patients who experience such loss of response.

Etanercept, Like other TNF inhibitors, is particularly indicated in patients with psoriatic arthritis, in whom improvement of symptoms often precedes response of psoriasis to treatment.

In clinical trials, the response of obese patients to treatment with fixed doses of biologics—including etanercept—tends to be suboptimal.⁴⁰ Analysis of a registry of Italian patients indicates that obese patients have a poorer initial response to systemic treatment for psoriasis, irrespective of the drug used.⁸³ In a certain percentage of patients, treatment with TNF inhibitors may be associated with an increase in weight (typically between 4 and 10 kg).^{84,85} This weight gain can be persistent in patients treated with etanercept,⁸⁵ and dietary recommendations should be made to affected patients.

When the recommendations of the SPC are followed, etanercept has a favorable safety profile and the requirements for patient monitoring are minimal.

Cost

The cost of the drug required to treat an average patient weighing 75 kg with etanercept for 24 weeks varies between €5682 and €8523 (price to retailer on www.portalfarma.com).

Table 5 summarizes the information and recommendations for etanercept.

Monoclonal Antibodies

Infliximab

Infliximab (Remicade, Schering-Plough), a chimeric monoclonal antibody formed by fusing human Ig constant regions to murine variable regions, binds specifically to TNF- α and is produced in genetically engineered CHO cells. Infliximab neutralizes the biological activity of TNF- α by binding with high affinity to all its forms (soluble and transmembrane). It produces apoptosis, complement-mediated cytotoxicity, and antibody-dependent cell-mediated cytotoxicity of cells that express TNF, all effects that may contribute to the drug's clinical efficacy.⁶¹ In Crohn disease, infliximab produces lymphocyte apoptosis, an effect that may explain its therapeutic action in this disease (not shared by etanercept).⁸⁶ The speed of the effect of this biologic on epidermal acanthosis has been attributed to keratinocyte apoptosis in psoriatic plaques.⁸⁷ In most patients, long-term maintenance of clinical response appears to depend on the presence of stable concentrations of drug until the following infusion. The mean half-life of infliximab is approximately 8.5 to 9 days,

although depending on the dose and duration of treatment infliximab may be detected in serum up to 28 weeks after infusion. The routes of elimination of infliximab are not all understood, but in patients with rheumatoid arthritis no age-related or weight-related differences have been observed.⁶¹

Infliximab is approved for the treatment of Crohn disease, ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis, and the "treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA."⁸⁸

Infliximab is supplied as a lyophilized powder in 100 mg vials. The vials must be stored between 2°C and 8°C and the powder reconstituted in water before dilution of the whole dose in 250 mL of 0.9% saline solution for infusion with a microfilter. The dosage regimen in the treatment of psoriasis is 5 mg/kg administered by intravenous infusion over a period of 2 hours, followed by additional doses of 5 mg/kg at weeks 2 and 6 and then every 8 weeks. When no response is obtained after 14 weeks (that is, after the patient has received 4 doses), treatment with infliximab should be discontinued.

Efficacy: Clinical Studies with Infliximab

1. *Short-term outcomes (10 weeks).* The efficacy of infliximab in inducing remission in patients with moderate to severe plaque psoriasis has been demonstrated in 2 randomized placebo-controlled clinical trials.⁸⁹⁻⁹¹ One of these included patients who had been treated with at least 1 systemic treatment prior to the study. Response to treatment occurs within 2 to 4 weeks of start of treatment, and peaks around week 10 in most cases.

A placebo-controlled pilot study of 33 patients investigated the effect of an induction regimen of 3 infusions of 5 or 10 mg/kg at weeks 0, 2, and 6.⁸⁹ At week 10, 82% of the patients receiving 5 mg/kg achieved a PASI 75 response (as compared to 18% of the placebo group). The higher dose was not associated with better efficacy at week 10.^{89,90} In the study by Gottlieb et al,⁹⁰ 33% of the patients receiving 5 mg/kg and 67% of those receiving 10 mg/kg maintained a PASI 75 response at week 26 (20 weeks after the last infusion); the corresponding percentages for a PASI 50 response were 40% and 73%, respectively.

The authors of a phase II trial involving 249 patients compared the responses obtained in 3 groups of patients who received induction therapy with either 3 or 5 mg/kg of infliximab or placebo.⁹¹ At week 10, 88% of the patients receiving 5 mg/kg, 72% of those receiving 3 mg/kg, and 6% of those receiving placebo had a PASI

Table 5. Etanercept: Summary and Recommendations

1.	Indication (EMA): treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA
2.	Date of approval: EMA 09/28/2004, FDA 09/24/2004
3.	Dose regimens: 50 mg once weekly or 25 mg twice weekly for 6 months, given subcutaneously; alternatively, 50 mg twice weekly can be administered during the first 3 months with response peaking at 3 months
4.	Clinical response: expected within 4-8 weeks, making etanercept a poor choice when rapid control of psoriasis is required, although a faster response can be achieved with initial high doses
5.	Short-term efficacy: 30%-49% of patients achieved a PASI 75 at 3 months (evidence level 1); 11%-22% of patients achieved a PASI 90 at 3 months (evidence level 1)
6.	Medium-term efficacy: 44%-71% of patients achieved a PASI 75 at 6 months (evidence level 1); 20%-42% of patients achieved a PASI 90 at 6 months (evidence level 1)
7.	Long-term efficacy: efficacy is sustained for up to 2.5 years in patients receiving long-term continuous treatment
8.	Contraindications: hypersensitivity to etanercept, active tuberculosis, sepsis or other serious infections, immunodeficiency, history of neoplastic disease, heart failure (NYHA functional class III-IV), and demyelinating disease. Do not administer live vaccines
9.	Adverse events: mildly pruritic injection site reactions may occur. Rare cases of the following adverse events have been reported: serious infections (eg, tuberculosis), malignancies, lupus erythematosus, cytopenia, demyelinating disease, and congestive heart failure.
10.	Baseline monitoring: standard laboratory workup, 2-step tuberculin skin test, hepatitis and HIV serology
11.	Ongoing monitoring during treatment: regular clinical assessment, and laboratory testing when needed at the discretion of the treating physician
12.	FDA pregnancy category: B
13.	<p>Other issues and recommendations:</p> <p>Response to high doses of etanercept may be suboptimal in very obese patients. The preferred treatment strategy in such patients is to use biologic agents that are administered using weight-adjusted dosage regimens</p> <p>Etanercept improves psoriatic arthritis and reduces the rate of progression of joint damage.</p> <p>Response to etanercept should be assessed at week 12, and the patient should be switched to an alternative treatment if an improvement of at least 50% of the baseline PASI has not been achieved.</p> <p>The efficacy of treatment at a dose of 25 mg twice weekly and 50 mg once weekly appears to be similar in most patients.</p> <p>Etanercept can be used as a cyclical treatment (6-month cycles) and this regimen is particularly indicated in patients with intermittent episodes of psoriasis; retreatments achieve the same efficacy as the first treatment and rebound does not occur.</p> <p>Screening for tuberculosis is particularly important before starting treatment with TNF inhibitors. This should include prior history of tuberculosis, recent contact with patients with tuberculous disease, purified protein derivative (PPD) skin test with a follow-up test 1 to 2 weeks later if the first test is negative¹⁰⁵ particularly in patients aged over 60 years and those with a history of treatment with cyclosporine, methotrexate, oral corticosteroids, or other immunosuppressants. Although the FDA do not recommend tuberculosis screening before treatment with etanercept because of the relatively minor risk of tuberculosis in patients treated with etanercept as compared to anti-TNF monoclonal antibodies,¹¹⁹ the higher prevalence of tuberculous infection in Spain makes such screening advisable. If inactive (latent) tuberculosis is diagnosed, anti-tuberculosis prophylactic therapy must be started 1 month before initiating treatment with etanercept, and in accordance with local recommendations. The tuberculin skin test may be repeated (if the initial test is negative) periodically (annually) and whenever exposure to tuberculosis is suspected.</p> <p>Patients should be warned about the risk of increased susceptibility to infection, and the appropriate diagnostic tests and early treatment should be carried out. In cases of serious infection (or major surgery with risk of infection) treatment with etanercept should be temporarily suspended.</p>

Abbreviations: EMA, *European Medicines Evaluation Agency*; FDA, *Food and Drug Administration*; HIV, *human immunodeficiency virus*; NYHA, *New York Heart Association*; PASI, *Psoriasis Area and Severity Index*; PPD, tuberculin skin test; PUVA, psoralen plus ultraviolet A radiation; TNF, tumor necrosis factor.

75. The corresponding percentages for a PASI 90 response were 58%, 46%, and 3%, respectively. When treatment was discontinued, the patients experienced

a progressive recurrence of the signs and symptoms of the disease that correlated with the decline in serum levels of infliximab. At week 26 (20 weeks after the last

Table 6. Summary of the Main Clinical Trials Undertaken with Infliximab 5 mg/kg (Results at Week 10)

Reference	Baseline Characteristics				PASI 75 Patients (%)	
	Drug		Placebo		Drug	Placebo
	N (% Male)	PASI: Mean (SD) or Mean (Range)	N (% Male)	PASI: Mean (SD) or Mean (range)		
Gottlieb et al 2004 ⁹¹	99 (73%)	20 (14-28)	51 (60.8%)	18 (15-27)	87 (87.9%)	3 (5.9%)
Reich et al 2005 ⁹²	301 (69%)	22.9 (9.3)	77 (79 %)	22.8 (8.7)	42 (80%)	2 (3%)
Menter et al 2007 ⁹³	314 (6.5%)	20.4 (7.5)	208 (69.2%)	19.8 (7.7)	237 (75.5%)	4 (1.9%)

Abbreviation: PASI, Psoriasis Area and Severity Index.

infusion), 33% of the patients in the group who received 5 mg/kg sustained a PASI 75 as compared to only 6% of the controls.

In a phase III trial that evaluated maintenance therapy for more than 1 year (the European Infliximab for Psoriasis Efficacy and Safety Study, EXPRESS), 301 patients received induction therapy with infliximab 5 mg/kg and continued to receive infusions every 8 weeks until week 46.⁹² At week 24, the 77 placebo-treated patients switched to induction and maintenance therapy with infliximab 5 mg/kg. The short-term results confirmed the efficacy findings of earlier trials: 80.4% of the treated patients achieved a PASI 75 at week 10 compared to 3% of the placebo group (intention-to-treat analysis); the corresponding percentages for PASI 90 were 57% and 1%, respectively. At week 10, 26% of patients achieved complete clearance (PASI 100). In another phase III trial including 835 patients with moderate to severe psoriasis, patients were randomly assigned to induction therapy (weeks 0, 2, and 6) with infliximab 3 mg/kg, 5 mg/kg, or placebo.⁹³ Irrespective of the response obtained, the infliximab-treated patients were randomized again at week 14 to either continuous (every 8 weeks) or intermittent (as needed) maintenance regimens at their induction dose. At week 10, 75.5% and 70.3% of the patients receiving 5 mg/kg or 3 mg/kg, respectively, achieved a PASI 75; the corresponding percentages for PASI 90 were 45.2% and 37.1%. The percentages at week 10 in the placebo group were 1.9% for PASI 75 and 0.5% for PASI 90.

The short-term results of the major clinical trials undertaken with infliximab are shown in Table 6.

The meta-analyses carried out indicate that the relative risk compared to placebo of achieving a PASI 75 at week 10 in patients receiving infliximab 5 mg/kg was 17.40 (95% CI, 6.41-47.19),²⁴ the risk difference with respect

to placebo was 0.77 (95% CI, 0.72-0.81),²⁵ and the number needed to treat to achieve a PASI 75 response was 2 (95% CI, 1.24-1.38).²⁴ At week 10, the relative risk of achieving a PASI 90 in patients receiving infliximab 5 mg/kg was 49.42 (95% CI, 16.01-152.54),²⁴ the risk difference with respect to placebo was 0.77 (95% CI, 0.71-0.81),²⁵ and the number needed to treat to achieve a PASI 90 response was 2 (95% CI, 1.67-2.31).²⁴

Two meta-analyses of placebo-controlled clinical trials showed the administration of infliximab to be the most effective of the interventions evaluated for the treatment of moderate to severe psoriasis.^{23,25}

2. *Results through weeks 24-26.* At the end of the placebo-controlled phase of the EXPRESS study (week 24), 82% of the patients receiving infliximab showed a PASI 75 response as compared to 4% of those receiving placebo; 88.6% of the patients who achieved a PASI 75 response by week 10 maintained it at week 24.⁹² In the study by Menter et al,⁹³ 78.0% and 64.5% of the patients treated continuously with 5 or 3 mg/kg, respectively, achieved a PASI 75 response by week 26; the corresponding percentages for a PASI 90 response were 56.0% and 33.3%. In the groups of patients treated intermittently after week 14, the rates through week 26 were 57.6% (5 mg/kg) and 42.0% (3 mg/kg) for PASI 75 and 23.6% (5 mg/kg) and 20.3% (3 mg/kg) for PASI 90.
3. *Long-term results (50 weeks).* In the EXPRESS study, the PASI 75 response was maintained by 82% of patients at week 24 and declined gradually thereafter. At week 50, however, 61% of the patients who started the study and 71% of those who completed the treatment according to protocol still had a PASI 75 response, and 45% and 55%, respectively, a PASI 90.⁹² Of the patients who achieved a PASI 75 at week 10, 73.6% maintained this response at week 50.

Menter et al⁹³ reported a PASI 75 at week 50 in 54.5% and 43.8%, respectively, of the patients treated continuously with 5 or 3 mg/kg, and a PASI 90 response in 34.3% and 25.0%, respectively. In the groups of patients treated intermittently after week 14, the rates through week 50 were 38.1% (5 mg/kg) and 25.4% (3 mg/kg) for PASI 75, and 10.4% (5 mg/kg) and 9.5% (3 mg/kg) for PASI 90.

In that study, the response obtained was better in the continuous treatment group than in the group of patients treated intermittently (as needed), irrespective of the dose used, and in the continuous treatment group better results were obtained with 5 mg/kg than with 3 mg/kg.

Special Considerations

1. *Loss of response.* The results of clinical trials indicate that a loss of response occurs in the long term (50 weeks) in approximately 25% of the patients who achieve a PASI 75 by week 10 after the induction phase.^{92,93}

It is clearly of great interest to identify this subgroup of patients who eventually experience a loss of response and to implement therapeutic strategies to rescue them when that happens because of the negative impact of relapse on patients who have achieved very significant clearance, sometimes for the first time since the onset of psoriasis symptoms. Rescue strategies could include shortening the interval between infusions, increasing the dose, reinduction, or adding low doses of methotrexate to the regimen to reduce the formation of antibodies that reduce infliximab levels.⁹⁴⁻⁹⁶

Preinfusion serum concentrations of infliximab were undetectable in between 26% and 29% of patients in the EXPRESS study. Loss of PASI 75 (25% among the patients with preinfusion serum infliximab concentrations) was associated in all patients with median concentrations below 1.0 #mg/mL and also correlated with the presence of antibodies to infliximab, which were detected in 61% of the patients who stopped responding as compared to 19% of those with a sustained response.⁹²

2. *Continuous versus intermittent (as needed) treatment.* The findings of the study by Menter et al⁹³ confirmed the need to use infliximab in patients with moderate to severe psoriasis as a long-term continuous treatment in order to optimize efficacy. There are indications that the response to repeated induction cycles or intermittent treatment (retreatment when a relapse of sufficient clinical severity occurs) is not as good as the response achieved with the first cycle of 3 injections and may be associated with a higher incidence of infusion reactions. In Crohn disease, the risk of the patient experiencing a loss of efficacy or developing resistance to treatment

(and anti-infliximab antibodies) is minimized with continuous treatment (compared to an intermittent regimen).⁹⁷ In patients with unstable psoriasis, the risk of adverse effects inherent in continuous maintenance treatment could be balanced by the advantages of such regimens.

3. *Combination therapy.* Infliximab has been used in combination with methotrexate to treat rheumatoid arthritis in large clinical trials. While the published clinical experience with combinations in the management of psoriasis is anecdotal, infliximab has been used in combination with methotrexate, cyclosporine, acitretin, and hydroxycarbamide. Such combinations may be useful for the following reasons: at the beginning of treatment to avoid abrupt withdrawal of prior treatment; when monotherapy with infliximab is not sufficiently effective; to reduce the dose of infliximab for cost reasons; or to enhance the efficacy of treatment with infliximab by reducing drug clearance and the formation of antibodies to infliximab, which may be associated with loss of response or the development of infusion reactions.

4. *Nail psoriasis.* Among the patients with nail psoriasis who participated in the EXPRESS study, clearance of this condition was achieved by 6.9%, 26.2%, and 44.7% at weeks 10, 24, and 50, respectively (compared to 5.1% of the placebo group at week 24).⁹⁸

5. *Psoriatic arthritis.* Patients with moderate to severe psoriasis and symptomatic psoriatic arthritis are particularly good candidates for treatment with infliximab and other TNF antagonists.

In clinical trials with infliximab, 61%, 39%, and 20% of patients achieved ACR 20, ACR 50, and ACR 70 ratings, respectively, at weeks 14-16 compared to 11%, 2%, and 1%, respectively, of the patients in the placebo group. However, no significant differences appear to exist between the different TNF inhibitors with respect to their effect on psoriatic arthritis.⁵⁷ Infliximab is the only anti-TNF agent for which data is available on efficacy in the treatment for dactylitis.⁹⁹

Safety

Infliximab is contraindicated in patients known to be hypersensitive to the drug, other murine proteins, or any of the excipients, in patients with tuberculosis or other serious infections, such as sepsis, abscesses, or opportunist infections, and in patients with moderate to severe heart failure (NYHA functional class III-IV). The presence of demyelinating disease and a history of malignancy should be ruled out before starting treatment with infliximab. Before, during, and after treatment with infliximab, all patients should be assessed for the presence of infection bearing in mind that the mean half-life of infliximab is approximately 10 to 20 days. If inactive

(latent) tuberculosis is diagnosed, antituberculosis prophylactic therapy must be started before initiating treatment with infliximab, and in accordance with local recommendations. Treatment with infliximab is contraindicated in pregnant women (FDA category B) or during breastfeeding.

The most commonly reported side effects associated with infliximab are headache, nausea, upper airway infections, and infusion reactions.⁸⁸ Infusion reactions have been reported in 3.8% to 27% of patients, although these have been mild in most cases. Guidelines for the management of infusion reactions have been published.¹⁰⁰⁻¹⁰² In the study by Menter et al,⁹³ 1 or more infusion reactions occurred (mild to moderate in most cases) in 9.6% of the patients receiving 3 mg/kg, 11.5% of those receiving 5 mg/kg, and in 5.8% of the patients receiving placebo. The corresponding percentages with respect to the total number of infusions carried out were 3.4%, 5.3%, and 2.2%. In the EXPRESS study,⁹² the rate of severe infusion reactions (those that led to withdrawal of treatment) was 1% in the patients receiving infliximab who were followed up through week 50.

In the EXPRESS study, a significant elevation of hepatic enzymes was reported in 9% of the patients receiving infliximab. This abnormality led to withdrawal of treatment in 3% of the participants and has made monitoring of this laboratory parameter essential.⁹²

Since worsening of pre-existing heart failure has been reported in patients receiving infliximab and other anti-TNF agents, these therapies should only be used with great caution in these patients. Infliximab is contraindicated in patients with debilitating heart failure (NYHA functional class III-IV).

Another concern is the risk of opportunist infections, including sepsis, and particularly reactivation of tuberculosis. Although the effect of infliximab on granuloma formation may explain the increased incidence of infections in patients treated with monoclonal antibodies compared to other anti-TNF agents,¹⁰³ proper application of screening techniques for latent tuberculosis (focused medical history, 2-step tuberculin skin testing, and chest radiograph) and the administration of isoniazid prophylaxis have helped reduce the incidence of tuberculosis in such cases in Spain, a country with a high prevalence of tuberculosis.^{104,105}

Infliximab should not be prescribed to patients with limb ulcers or evidence of active infection, and any kind of febrile or infectious process during treatment must be viewed with a high index of suspicion and be treated by promptly starting antibiotic therapy to prevent the development of pneumonia, sepsis, or other infectious complications. In principle, treatment with infliximab and

other anti-TNF agents is contraindicated in patients who are HIV positive or have active hepatitis B or C. However, at the discretion of the treating physician, treatment may be contemplated in patients with HIV or hepatitis C infection who are undergoing appropriate treatment; reactivations have been reported in patients with chronic hepatitis B receiving infliximab.¹⁰⁶

The formation of antinuclear antibodies has been reported in a significant percentage of patients (56% in a cohort of patients with Crohn disease treated for 1 year¹⁰⁷). In a small number of cases, these antibodies may be associated with the development of symptoms similar to drug-induced lupus erythematosus and other autoimmune diseases. Because the development of demyelinating disease has been reported in isolated cases, any suggestive symptom should be investigated, and the administration of anti-TNF agents is contraindicated in patients with a history of multiple sclerosis or other demyelinating diseases. Patients with a family history of demyelinating disease have an increased risk of developing such disease and are therefore not good candidates for this type of therapy.

The possible relationship between treatment with TNF antagonists and the development of malignancy is still a matter of debate. In early studies, an increased risk of developing lymphoma was detected in patients with rheumatoid arthritis receiving infliximab and other anti-TNF agents. However, patients with rheumatoid arthritis already have an elevated risk of lymphoma, and recent studies were unable to establish the existence of a differential risk with respect to other TNF antagonists.¹⁰⁸ Some authors have reported hepatosplenic T-cell lymphoma in young patients with Crohn disease receiving infliximab in combination with azathioprine or mercaptopurine. Although this malignancy has also been reported in patients receiving monotherapy with these immunosuppressants, it has been included in the SPC.

A meta-analysis of malignancies in placebo-controlled clinical trials with adalimumab or infliximab in patients with rheumatoid arthritis reported a dose-dependent odds ratio for malignancy of 3.3 (95% CI, 1.2-91),¹⁰⁹ while a Swedish study that compared patients with rheumatoid arthritis with the normal population detected an increase in the standardized incidence of nonmelanoma skin cancer of 3.3 (95% CI, 1.1-7.8) between 1 and 2 years after start of treatment,¹¹⁰ although no differences were found in the risk of developing other cancers. No similar studies are available in patients with psoriasis.

Clinical Management

Infliximab is indicated for induction and maintenance treatment of moderate to severe psoriasis and is the drug with the best response rate up to 12 weeks (PASI 75 in

76%-80% of patients at week 12, PASI 90 in 45%-57% at week 10).

Because of the speed of onset of clinical effect achieved with infliximab (PASI 50 within approximately 2 weeks), it is an excellent choice when the therapeutic objective is to achieve rapid disease control (for example in cases of severe inflammatory flares). Continuous treatment is preferable to intermittent treatment because it affords greater efficacy and possibly a lower risk of infusion reactions and loss of response in the case of retreatment. Infliximab should, therefore, be considered as a long-term treatment particularly suitable for patients with continuous disease activity.

Loss of response in the long term occurs in a significant percentage of patients, although this can be prevented in some cases by increasing the dose or the frequency of administration (for example reducing the interval between infusions from 8 to 6 weeks), by combining with methotrexate or other systemic therapies,⁹⁴ or by repeating the induction therapy.⁹⁶

Because infliximab is administered in a weight-adjusted dose, no loss of efficacy is observed in obese patients.

Like the other anti-TNF inhibitors, infliximab is particularly indicated in the treatment of patients with psoriatic arthritis.

The chief adverse events associated with infliximab are infusion reactions, usually acute and mild to moderate in intensity. The treatment of these reactions is standardized, and they can be prevented by slowing down the rate of infusion and administering premedication and low doses of methotrexate.¹⁰²

Cost

The cost of the drug required to treat an average patient weighing 75 kg with infliximab for 24 weeks is €10 726 (price to retailer on www.portalfarma.com).

Table 7 summarizes the information and recommendations for infliximab.

Adalimumab

Adalimumab (Humira, Abbott) is the first fully human anti-TNF IgG antibody produced in genetically engineered CHO cells. The mechanism of action and binding properties of adalimumab are similar to those of infliximab; each adalimumab molecule can bind up to 2 TNF trimers, and a single TNF trimer can bind to up to 3 adalimumab molecules. The estimated bioavailability of adalimumab following a single subcutaneous dose of 40 mg is 64%, and the approximate half-life is 2 weeks (range, 10-20 days).^{60,61} Methotrexate reduces the clearance of adalimumab following single and multiple doses by 29% and 44%, respectively.¹¹¹

Adalimumab is indicated in the treatment of rheumatoid arthritis (in monotherapy or in combination with methotrexate), polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, and "moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA."¹¹²

It is supplied in the form of a solution for injection in a pre-filled pen (40 mg): each pack contains 2 pens. The recommended dose of adalimumab for adult patients with moderate to severe psoriasis is an initial dose of 80 mg in week 0 followed by 40 mg every other week, starting the week after the initial dose. The drug is self-administered by the patient. Continuation of therapy after 16 weeks should be carefully reconsidered in patients in whom treatment has not produced any response during this period.

Efficacy

The efficacy and safety of adalimumab have been studied in 2 recently published pivotal phase III clinical trials.^{113,114} In both those studies, the primary efficacy endpoint was the percentage of patients achieving at least a PASI 75 response by week 16.

1. *Short-term results (16 weeks)*. The first of these trials (the Randomized Controlled Evaluation of Adalimumab Every Other Week Dosing in Moderate to Severe Psoriasis Trial, or REVEAL study) evaluated 1212 patients over 3 treatment periods to determine the efficacy in the short (1-16 weeks, period A) and long term (16-33 weeks, period B) and to investigate the loss of satisfactory response when treatment was interrupted compared to the results obtained with continuous treatment (period C).¹¹³ The results at week 16 showed an effective outcome (PASI 75) rate of 71% (578 of 814) in the patients treated with adalimumab as compared to 7% (26 of 398) in the group receiving placebo. The percentages for a PASI 90 and PASI 100 (complete clearance) were 45% and 20% in the group treated with adalimumab, and 2% and 1% in the placebo group, respectively.

The Comparative Study of Humira vs Methotrexate vs Placebo in Psoriasis Patients (the CHAMPION study) was the first clinical trial to compare a biologic agent with a traditional systemic treatment in patients with psoriasis.¹¹⁴ A total of 271 patients were randomized to receive adalimumab, methotrexate (at an initial dose of 7.5 mg with the possibility of increasing the dose up to a maximum of 25 mg depending on the patient's tolerance and need), or placebo. At week 16, 79.6% of

Table 7. Infliximab: Summary and Recommendations

1. Indication (EMA): treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA
2. Date of approval: EMA 10/04/2005, FDA 09/26/2006
3. Dose regimens: induction therapy with 5 mg/kg at weeks 0, 2, and 6 followed by administration every 8 weeks; dose and interval between infusions may be adjusted as required at the discretion of the clinician.
4. Clinical response: expected within 1-2 weeks, making infliximab the biologic agent of choice (unless contraindicated) when rapid disease control is desired
5. Short-term efficacy: 76%-80% of patients achieved a PASI 75 at week 10 (evidence level 1); 45%-57% of patients achieved a PASI 90 by week 10 (evidence level 1.)
6. Medium-term efficacy: 78%-82% patients achieved a PASI 75 at 24-26 weeks (evidence level 1); 56%-58% of patients achieved a PASI 90 at 24-26 weeks (evidence level 1)
7. Long-term efficacy (50 weeks): 54%-61% of patients sustained a PASI 75 response at week 50 (evidence level 1); 34%-45% of patients sustained a PASI 90 response at week 50 (evidence level 1)
8. Contraindications: hypersensitivity to infliximab, active tuberculosis, sepsis or other serious infections, immunodeficiency, history of malignant disease, heart failure (NYHA functional class III-IV), and demyelinating disease. Do not administer live vaccines
9. Adverse events: infusion reactions (more common in patients who have developed antibodies to infliximab); the incidence of such reactions can be reduced by concomitant administration of methotrexate 5-10 mg/wk. There have been rare reports of serious infections (eg, tuberculosis), and the following adverse events have also been reported: elevated transaminase, lupus-like syndrome, cytopenia, demyelinating disease, and exacerbation or new onset of congestive heart failure.
10. Baseline monitoring: standard laboratory workup, 2-step tuberculin skin test, hepatitis and HIV serology
11. Monitoring during treatment: regular clinical assessment, laboratory testing as needed
12. FDA pregnancy category: B
13. Other issues and recommendations: <p>Infliximab must be administered in a hospital setting, and particular attention must be paid to the risk of infusion reactions. Detailed protocols have been published for the diagnosis, treatment, and prevention of such reactions. Infusion reactions do not necessarily lead to withdrawal of treatment.</p> <p>Infliximab improves psoriatic arthritis and reduces the rate of progression of joint damage</p> <p>Response to infliximab should be assessed at week 12, and the patient should be switched to an alternative treatment if an improvement of at least 50% of the baseline PASI has not been achieved.</p> <p>It is generally preferable to plan a long-term continuous regimen from the beginning; intermittent therapy is associated with a poorer clinical response and a higher incidence of infusion reactions.</p> <p>Loss of response occurs in 25% of patients after 1 year of treatment. Based on clinical criteria, the dose or frequency of administration may be adjusted in such cases and/or the biologic regimen complemented by low doses (5-10 mg/wk) of methotrexate.</p> <p>In patients with joint disease and in retreatments it may be advisable to complement the biologic regimen with low doses (7.5-10 mg/wk) of methotrexate.</p> <p>Screening for tuberculosis is particularly important before starting treatment with TNF inhibitors. This should include history of tuberculosis, recent contact with patients with tuberculous disease, purified protein derivative (PPD) skin test with a follow-up test 1 to 2 weeks later if the first test is negative¹⁰⁵ particularly in patients aged over 60 years and those with a history of treatment with cyclosporine, methotrexate, oral corticosteroids, or other immunosuppressants. When latent tuberculosis is diagnosed, antituberculosis prophylactic therapy must be started 1 month before initiating treatment with etanercept, and in accordance with local recommendations. The tuberculin skin test may be repeated (if the initial test is negative) periodically (annually) and whenever exposure to tuberculosis is suspected.¹¹⁹</p> <p>Patients should be warned about the risk of increased susceptibility to infections, and the appropriate diagnostic tests and early treatment should be carried out. In cases of serious infection (or major surgery with risk of infection) treatment with infliximab should be temporarily suspended.</p>

Abbreviations: EMA, *European Medicines Evaluation Agency*; FDA, *Food and Drug Administration*; HIV, *human immunodeficiency virus*; NYHA, *New York Heart Association*; PASI, *Psoriasis Area and Severity Index*; PPD, tuberculin skin test; PUVA, psoralen plus ultraviolet A radiation; TNF, tumor necrosis factor.

the patients receiving adalimumab achieved a PASI 75 response compared to 35.5% of the group receiving methotrexate and 18.9% of the controls. Response to adalimumab was rapid, with a mean percent PASI improvement from baseline of 57% at week 4, rising to around 81% by week 16. The corresponding percentages for PASI 90 and PASI 100 (complete clearance) were 51.3% and 16.7%, respectively, in the group receiving adalimumab, and 11.3% and 1.3% in the placebo group.

Only 1 meta-analysis²⁵ has included data from a clinical trial of adalimumab in psoriasis.¹¹³ The risk difference with respect to placebo of achieving a PASI 75 response was 0.64 (95% CI, 0.61-0.68),²⁵ and the number needed to treat to achieve a PASI 75 was 2 (95% CI, 1.47-1.64 [calculated using the data from the study by Schmitt et al²⁵]). According to this meta-analysis, adalimumab was significantly more effective than the other biologic agents (with the exception of infliximab) and cyclosporine. The characteristics of these trials are summarized in Table 8.

2. *Results after 24 weeks.* At week 24 of the REVEAL study (which included an open-label extension phase after week 16), 70% of patients achieved a PASI 75 and 49% a PASI 90 response.¹¹³
3. *Long term.* Maintaining the clinical response obtained with adalimumab was the objective of a number of open-label extension studies that included all the patients who participated in the phase II¹¹⁵ and phase III trials. The data published to date indicate that the response to adalimumab was maintained until week 120 in the patients receiving continuous treatment, with PASI 75 response rates in 77.6% of the patients (n=92).¹¹⁶ The percentages for PASI 90 and PASI 100 responses at week 120 were 53.1% and 28.6%, respectively. The long-term safety and efficacy results for the patients in the REVEAL study who received continuous treatment with adalimumab for 18 months

were published recently.¹¹⁷ Of the 233 patients included in this open-label extension, 228 (98%) completed the 18 months of treatment, achieving a PASI 75 efficacy rate of 87%. The percentages for PASI 90 and PASI 100 were 63% and 34%, respectively.

Special Considerations

1. *Loss of response.* All the patients in the REVEAL study who had a PASI 75 response at week 33 and who were assigned to the adalimumab group in period A were once again randomized in period C to receive adalimumab (continuous treatment) or placebo (withdrawal of treatment) for a further 19 weeks. At week 52 (the end of period C), 28% of the patients with a PASI 75 who had been reassigned to placebo experienced a loss of satisfactory response between weeks 33 and 52, while only 5% of the patients receiving continuous treatment with adalimumab experienced a loss of satisfactory response ($P < .001$).¹¹³ (Loss of satisfactory response was defined as an improvement from baseline in the PASI score of less than 50% and an increase in PASI of at least 6 points with respect to week 33.) Anti-adalimumab antibodies were detected in 77 out of 920 (8.4%) of the patients receiving adalimumab as monotherapy for psoriasis. Because the analyses of immunogenicity are specific to each product, it is not possible to compare antibody rates between different biologic agents. The formation of anti-adalimumab antibodies is associated with a reduction in efficacy. In the REVEAL study, 3 out of 7 patients (43%) with anti-adalimumab antibodies experienced a loss of satisfactory response compared to 65 out of the 233 antibody-negative patients (28%).¹¹³ There appears to be no correlation between the presence of anti-adalimumab antibodies and the presence of adverse effects.
2. *Retreatment.* At the end of period C in the REVEAL study, the patients could continue (or

Table 8. Adalimumab: Summary of the Chief Placebo-Controlled Clinical Trials (Results at Week 16)

Reference	Baseline Characteristics				PASI 75 Patients (%)	
	Drug		Placebo		Drug	Placebo
	No (% Male)	PASI, Mean (SD)	No (% Male)	PASI, Mean (SD)		
Menter et al 2008 ¹¹³	814 (67.9%)	19.0 (7.1)	398 (64.6%)	18.8 (7.1)	578 (71.0%)	26 (6.5%)
Saurat et al 2008 ¹¹⁴	108 (64.8%)	20.2 (7.5)	53 (66.0%)	19.2 (6.9)	86 (79.6%)	10 (18.9%)

Abbreviation: PASI, Psoriasis Area and Severity Index

resume) treatment with adalimumab 40 mg every 2 weeks for a further 6 months irrespective of whether they were assigned to the treatment or the placebo (suspension of treatment) group during period C. Only 55% of the patients who lost a satisfactory response during period C achieved a PASI 75 response after a further 6 months of treatment or retreatment, while 5 out of 6 of those who sustained a satisfactory response achieved a PASI 75 (irrespective of whether treatment was interrupted or not).^{113,118}

3. *Obesity.* There are no published data that allow us to draw valid conclusions concerning any difference in response in obese patients treated with adalimumab.
4. *Psoriatic arthritis.* Adalimumab is also indicated in the treatment of active and progressive psoriatic arthritis in adults in whom the response to prior therapy with disease-modifying antirheumatic drugs has proved inadequate. Patients with moderate to severe psoriasis and symptomatic psoriatic arthritis are particularly good candidates for treatment with adalimumab and other TNF antagonists.

In the clinical trials carried out with adalimumab, 58% of the patients receiving the active drug achieved an ACR 20 rating at week 12 compared to 14% in the placebo group, and this response was sustained through week 24 and up to week 48 in the extension study. In any case, the results of all of the recently published meta-analyses appear to indicate that there are no significant differences between the various TNF inhibitors with respect to their effect on psoriatic arthritis.⁵⁷

Safety

Adalimumab is contraindicated in patients known to be hypersensitive to the drug or any of the excipients, in patients with tuberculosis or other serious infections, such as sepsis, abscesses, or opportunist infections, and in patients with moderate to severe heart failure (NYHA functional class III-IV). The presence of demyelinating disease and a history of malignancy should be ruled out before starting treatment with adalimumab. Before, during, and after treatment with adalimumab, all patients should be assessed for the presence of infection bearing in mind that the mean half-life of adalimumab is approximately 10 to 20 days. If inactive (latent) tuberculosis is diagnosed, antituberculosis prophylactic therapy must be started before initiating treatment with adalimumab and in accordance with local recommendations. Treatment with adalimumab is not recommended in pregnant women (FDA category B) or during breastfeeding.

The safety profile of adalimumab is similar to that of the other TNF antagonists. In the pivotal controlled clinical trials, 14% of the patients receiving adalimumab developed injection site reactions (erythema and/or pruritus, bleeding, pain, or swelling) compared to 8% of the patients who received placebo or the active comparator.¹¹⁰ During the clinical trials, an increased risk of developing serious infection was detected in patients receiving adalimumab, and this finding was subsequently confirmed by postmarketing reports. Infections such as pneumonia, pyelonephritis, septic arthritis, and septicemia are particularly important. There have been reports of tuberculosis and massive opportunist infections in patients receiving adalimumab. Most of the cases of tuberculosis were extrapulmonary (disseminated disease) and occurred during the first 8 months after start of treatment; this timing could be interpreted as an indication of reactivation of latent infection.

Reactivation of hepatitis B virus has been reported in chronic carriers of the disease treated with TNF inhibitors including adalimumab, with a fatal outcome in some cases. Before starting treatment with adalimumab, or any other TNF inhibitor, patients should be assessed for possible prior infection with hepatitis B virus. Treatment with adalimumab must be discontinued if a reactivation of the hepatitis B virus occurs and an effective antiviral therapy should be started complemented by appropriate support therapy.

In the controlled clinical trials with TNF antagonists, more cases were reported of malignancies—including lymphomas—in patients with rheumatoid arthritis treated with anti-TNF than in the control group. However, patients with rheumatoid arthritis already have an elevated risk of lymphoma, and recent studies were unable to establish the existence of a differential risk with respect to other TNF antagonists.¹⁰⁸ In the clinical trials carried out with adalimumab for various indications, the incidence of nonmelanoma skin cancer was 8.8 per 1000 patient-years among patients receiving adalimumab and 2.6 per 1000 patient-years among the controls.¹¹² For this reason, all patients, and particularly those who have received prior treatment with immunosuppressants and psoriatic patients who have been treated with PUVA, must be examined to detect the presence of nonmelanoma skin cancer before and during treatment with adalimumab.¹¹²

Cost

The cost of the drug required to treat an average patient weighing 75 kg with adalimumab for 24 weeks is €7486 (price to retailer on www.portalfarma.com).

Table 9 summarizes the information and recommendations for adalimumab.

Clinical Management

Adalimumab is indicated in induction and maintenance treatment of moderate to severe psoriasis, achieving a rate of response of 68% to 77% for PASI 75 and 37% to 48% for PASI 90 at week 12. The corresponding

percentages at week 16 are 71% to 80% and 45% to 51%, respectively.^{113,114}

Because of the speed of onset of clinical effect achieved with adalimumab (PASI 50 within 2 to 4 weeks) it is an excellent choice when rapid disease control is required. No data are available concerning intermittent treatment

Table 9. Adalimumab: Summary and Recommendations

1.	Indication (EMA): treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate, or PUVA
2.	Date of approval: EMA 12/19/2007, FDA 01/18/2008
3.	Dose regimens: 80 mg in the first week, 40 mg the second week, followed by 40 mg every other week thereafter, given subcutaneously
4.	Clinical effect: expected within 2-4 weeks
5.	Short-term efficacy: 71%-80% of patients achieved a PASI 75 at week 16 (evidence level 1); 45%-51% of patients achieved a PASI 90 at week 16 (evidence level 1)
6.	Medium-term efficacy: 70% of patients achieved a PASI 75 at week 24 (evidence level 2); 49% of patients achieved a PASI 90 at week 24 (evidence level 2)
7.	Long-term efficacy (18 months): 87% of patients sustained a PASI 75 response at 18 months (evidence level 2); 63% of patients sustained a PASI 90 response at 18 months (evidence level 2)
8.	Contraindications: hypersensitivity to adalimumab, active tuberculosis, sepsis or other serious infections, immunodeficiency, history of malignant disease, heart failure (NYHA functional class III-IV), and demyelinating disease. Do not administer live vaccines
9.	Adverse events: moderately painful injection site reactions There have been rare reports of serious infections (eg, tuberculosis), and the following have also been reported: elevated transaminase, lupus-like syndrome, cytopenia, demyelinating disease, and exacerbation or new onset of congestive heart failure.
10.	Baseline monitoring: standard laboratory workup, 2-step tuberculin skin test, hepatitis and HIV serology
11.	Monitoring during treatment: regular clinical assessment, laboratory testing as needed
12.	FDA pregnancy category: B
13.	Other issues and recommendations: Adalimumab improves psoriatic arthritis and reduces the rate of progression of joint damage. Response to adalimumab should be assessed at 16 weeks, and the patient should be switched to an alternative treatment if an improvement of at least 50% of the baseline PASI has not been achieved. It is generally preferable to plan a long-term continuous regimen from the beginning; intermittent therapy is associated with loss of response in 28% of patients. Loss of response occurs in 5% of patients after 1 year of treatment. When response is lost, continuation of treatment or retreatment for 6 months achieves a PASI 75 response in only 55% of cases. Screening for tuberculosis is particularly important before starting treatment with TNF inhibitors. This should include history of tuberculosis, recent contact with patients with tuberculous disease, purified protein derivative (PPD) skin test with a follow-up test 1 to 2 weeks later if the first test is negative ¹⁰⁵ particularly in patients aged over 60 years and those with a history of treatment with cyclosporine, methotrexate, oral corticosteroids, or other immunosuppressants. When latent tuberculosis is diagnosed, antituberculosis prophylactic therapy must be started 1 month before initiating treatment with adalimumab, and in accordance with local recommendations. The tuberculin skin test may be repeated (if the initial test is negative) periodically (annually) and whenever exposure to tuberculosis is suspected. ¹¹⁹ Patients should be warned about the risk of increased susceptibility to infections, and the appropriate diagnostic tests and early treatment should be carried out. In cases of serious infection (or major surgery with risk of infection) treatment with adalimumab should be temporarily suspended.

Abbreviations: EMA, European Medicines Evaluation Agency ; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; NYHA, New York Heart Association; PASI, Psoriasis Area and Severity Index ; PPD, tuberculin skin test; PUVA, psoralen plus ultraviolet A radiation; TNF, tumor necrosis factor.

Table 10. Main Efficacy and Safety Parameters of the Biologic Therapies Used in the Treatment of Moderate to Severe Psoriasis

	<i>Efalizumab</i> ²⁹⁻³⁴	<i>Etanercept</i> ^{63,64}	<i>Etanercept</i> ^{64,65}	<i>Etanercept</i> ⁶⁶	<i>Infliximab</i> ⁹¹⁻⁹³	<i>Adalimumab</i> ^{113,114}
Approximate elimination half-life	6 days	4 days			9 days	15 days
Dose	0.7 mg/kg SC 1st dose, 1 mg/kg/wk	25 mg SC twice weekly for 24 weeks	50 mg SC twice weekly for 12 weeks, (then 25 mg twice weekly until week 24)	50 mg SC once weekly for 24 weeks	5 mg/kg IV induction therapy in weeks 0, 2, and 6 and then every 8 weeks	80 mg SC 1st dose, 40 mg weekly, then 40 mg every 2 weeks
Onset of clinical effect usually occurs within:	4-8 weeks	4-8 weeks	4-8 weeks	4-8 weeks	1-2 weeks	2-4 weeks
PASI 75 efficacy at 10-16 weeks ^a	22%-39% 12 weeks	30%-34% 12 weeks	49% 12 weeks	38% 12 weeks	76%-80% week 10	71%-80% 16 weeks
PASI 75 efficacy at 24-26 weeks	44% 44%-56% 24 weeks	54% 24 weeks	71% 24 weeks	82% 24 weeks	76% 26 weeks	70% 24 weeks
Eficacia PASI90 a 10-16 weeks	Sin datos	11-12% 12 weeks	21-22% 12 weeks	14% 12 weeks	57% 10 weeks	45-51% 16 weeks
ASI 90 efficacy at 24-26 weeks	No data	20%-21% 24 weeks	No data	42% 24 weeks	58% 24 weeks 56% 26 weeks	49% 24 weeks
Duration of remission (median) ¹²⁰	84 days	70-90 days		No data	140 days after the induction	No data
Long-term treatment	Sustained response	Sustained response; studies with different doses (50 mg/wk, 50 mg twice weekly)		No datas	54-61% PASI75 34-45% PASI90 a las 50 weeks	87% PASI75 63% PASI90 a los 18 meses
Most common adverse effects	Flu-like symptoms, high white blood cell and lymphocyte counts	Injection site reactions			Infusion reactions	Injection site reactions
Chief risks ^b	Exacerbation or rebound of psoriasis, thrombopenia, infections	Tuberculosis and other infections			Tuberculosis and other infections	Tuberculosis and other infections

Source: references 18-25, 29-34, 63-66, 91-93, 113, and 114

^aAbsolute efficacy rates in the treatment group; short-term differential efficacy rates (with respect to placebo) can be calculated from the data in the tables with data for each agent. ^bGuidelines have recently been published on the subject of treatment monitoring and the use of vaccinations in patients receiving biologics for psoriasis.¹¹⁹ Live and attenuated vaccines (varicella-zoster or yellow fever in adults) are contraindicated in these patients.

Abbreviations: IV, intravenous administration; SC, subcutaneously; PASI, Psoriasis Area and Severity Index.

or retreatment with adalimumab, although it is known that 28% of patients lose a satisfactory response within 19 weeks of discontinuation of treatment.

Adalimumab should, therefore, generally be considered as a continuous treatment in psoriasis; 28% of patients

lose a satisfactory response when treatment is suspended. Although response to treatment is generally sustained in the long term, loss of response does occur in a small percentage of patients (5%) receiving continuous treatment for 1 year. The possible effect of an increase in

the frequency of administration or of combined treatment with methotrexate or other systemic treatments is unknown.

Only 55% of the patients who experience a loss of satisfactory response to treatment with adalimumab achieve a PASI 75 response after 6 months of additional treatment or retreatment after suspension of treatment.

The possible difference in clinical response to treatment with adalimumab among obese patients is unknown.

Like the other TNF inhibitors, adalimumab is particularly indicated in the treatment of patients with psoriatic arthritis.

Choice of Treatment

Table 10 summarizes the principal efficacy and safety parameters relating to the different biologic agents used to treat moderate to severe psoriasis. In any event, none of the biologic agents discussed in these guidelines should be considered a first-line option solely on the basis of the response rates published in clinical trials. The decision to use a particular biologic agent should be made on a case-by-case basis taking into account characteristics such as the age, sex, and weight of the patient, associated comorbidities, the presence of arthritis, as well as the past history and current characteristics of the psoriasis. The physician must also decide whether treatment should be intermittent or continuous in the long term depending on whether disease activity is intermittent or continuous and the past need for systemic treatment.

Final Note

The present guidelines do not represent an exhaustive review of the bibliography and the SPCs of the drugs discussed, and the discussion focuses primarily on the practical aspects of treatment and the choice of drug. The prescribing physician should read the instructions in the EMEA SPC carefully and compare them with the recommendations in this consensus statement, particularly with regard to dose, contraindications, and possible interactions. The authors would welcome any feedback from readers who may detect errors in these guidelines or have new information that should be included in future updated versions.

Conflicts of Interest

The authors have participated in clinical trials, have served as consultants, have been remunerated for attending or speaking at conferences, and have received sponsorship

to attend training events from Abbott, Merck-Serono, Wyeth, and Schering-Plough.

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Addendum

On February 19, 2009, while the present manuscript was in press, the European Medicines Agency (EMA) recommended the suspension of the marketing authorization for Raptiva because of safety concerns including the risk of progressive multifocal leukoencephalopathy in patients receiving this drug. Efalizumab has, therefore, been withdrawn from the market because it is considered that the therapeutic benefit no longer outweighs the risks associated with the administration of this drug. In the case of etanercept, the Summary of Product Characteristics has been modified to include the possibility of continuous treatment and the treatment of pediatric patients (8 years and older) at a dose of 0.8 mg/kg.

[<http://www.emea.europa.eu/humandocs/Humans/EPAR/raptiva/raptiva.htm>].