

CONSENSUS STATEMENT

Consensus Document on the Evaluation and Treatment of Moderate to Severe Psoriasis. Spanish Psoriasis Group* of the Spanish Academy of Dermatology and Venereology

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Abstract. The treatment of psoriasis has been revolutionized by the introduction of biologic agents; these agents achieve skin clearance and long-term improvement without the risk of toxicity that has limited use of the traditional systemic treatments. The role of systemic treatment in the management of psoriasis is being reviewed on the basis of a large volume of scientific evidence on the efficacy and safety of biologic agents, and new therapeutic goals and strategies are being devised for patients with moderate to severe psoriasis. This has led to the need to establish severity criteria that will provide the rationale for the indication of the different systemic agents currently available for the treatment of moderate to severe psoriasis, as well as therapeutic goals, efficacy measures, therapeutic strategies, screening protocols, and choice of treatment based on the risk-benefit ratio of the different agents. These criteria must be established through consensus by experienced dermatologists and based on available scientific evidence. The present document reflects the consensus of the Spanish Psoriasis Group on these different issues in the management of moderate to severe psoriasis.

Key words: psoriasis, treatment, consensus, criteria, biologic agents.

DOCUMENTO DE CONSENSO SOBRE LA EVALUACIÓN Y EL TRATAMIENTO DE LA PSORIASIS MODERADA/GRAVE DEL GRUPO ESPAÑOL DE PSORIASIS* DE LA ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

Resumen. El tratamiento de la psoriasis se ha visto revolucionado por la introducción de los agentes biológicos, que permiten obtener blanqueamientos y mejorías a largo plazo sin el riesgo de toxicidad que ha venido limitando el tratamiento de estos pacientes con agentes sistémicos clásicos. 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 establecer 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 basada en la evidencia científica disponible, criterios de gravedad que justifiquen la indicación de los diferentes tratamientos sistémicos actualmente disponibles para la psoriasis, así como objetivos terapéuticos y parámetros de eficacia, estrategias de tratamiento, cribaje de los pacientes y selección del tratamiento basada en criterios de beneficio/riesgo. El presente documento recoge el consenso del

Grupo Español de Psoriasis en estos diferentes aspectos del manejo de la psoriasis moderada a grave..

Palabras clave: psoriasis, tratamiento, consenso, criterios, agentes biológicos.

*The Spanish Psoriasis Group is a working group of the Spanish Academy of Dermatology and Venereology. The 50 members of the group are dermatologists working in hospital settings who have special expertise in the treatment of patients with psoriasis and are involved in clinical and therapeutic research in this specialized area.

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Introduction

Psoriasis is a chronic recurrent skin disease that affects 1.4% of the Spanish population.¹ Although the cutaneous manifestations of psoriasis are only life-threatening in

exceptional cases of erythrodermic or pustular psoriasis, the disease has significant physical, emotional, sexual, work-related, and financial repercussions, significantly reducing the patient's quality of life with an impact similar to that of diabetes, arthritis, or chronic obstructive pulmonary disease.² Psoriasis is associated with potentially disabling arthropathy in a significant proportion of patients (11% in a telephone survey carried out in the United States of America³ and 12.8% in a survey of dermatologists in Spain and Portugal⁴) and with important comorbidities⁵ including metabolic syndrome and increased cardiovascular risk. The comorbidities correlate with disease severity and increase the risk of mortality in these patients, especially during the most productive years of life.⁶

Treatment of moderate to severe psoriasis is difficult owing to the variability of clinical response and the adverse effects associated with conventional systemic therapy. Most patients were dissatisfied with treatment and there was a demand for more effective therapies.⁷ As current psoriasis treatments suppress rather than cure the disease, long-term continuous therapy is required to achieve acceptable control of the signs and symptoms in most patients. Moreover, the achievement of such control with traditional systemic treatments and photochemotherapy is associated with a significant risk of cumulative toxicity (kidney or liver damage, teratogenicity, and increased risk of developing neoplasms). Because of the side effects they cause, traditional systemic therapies are further limited by the comorbidities associated with the disease,⁸ such as dyslipidemia, hypertension, obesity associated with metabolic syndrome, fatty liver, and alcoholism.

Thanks to advances in our understanding of the pathophysiology of psoriasis, new therapeutic strategies have recently been identified. The mechanism of action of the biologic agents available since 2004 is to block the surface molecules involved in the activation and migration of inflammatory cells and to inhibit proinflammatory mediators. These new treatments are free from the organ-specific toxicity associated with traditional systemic psoriasis treatments. The European Medicines Agency (EMA) has approved the biologic agents efalizumab, etanercept, infliximab, 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 conventional systemic therapy.

The present consensus document was drafted by a group of dermatologists with particular expertise in the treatment of moderate to severe psoriasis with both conventional systemic therapies and biologic agents. All of those involved were members of the Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology. Once drafted, the document was reviewed by all the members of the group and discussed until consensus was reached on the definition of the severity

of psoriasis, indications for treatment, treatment response, and strategies for treatment with conventional systemic medication and biologic agents in Spain.

Severity Criteria

The measures normally used to assess the severity of psoriasis in dermatological practice are the proportion of the body surface area (BSA) affected and the Psoriasis Area and Severity Index (PASI). It is generally accepted that patients with a greater than 5% affected BSA have moderate to severe psoriasis⁹ and in most recent clinical trials a PASI above 10 or 12 has been used as an inclusion criteria to define moderate to severe psoriasis. An affected BSA greater than 10% and a PASI score of 12 or higher have been proposed as criteria for severe psoriasis for use in clinical trials.¹⁰ While some authors define moderate psoriasis as a PASI between 7 and 12 and severe psoriasis as a PASI higher than 12,¹¹ others prefer to use the "rule of tens" criteria, which define severe psoriasis as a PASI higher than 10, an affected BSA of more than 10%, or a Dermatology Life Quality Index (DLQI) score greater than 10.¹²

When using quality-of-life indices to assess psoriasis clinicians should remember that, even when an instrument has been validated, cultural differences exist that limit the validity of a least some of the tools currently available.¹³ Consequently, we need to develop new instruments for measuring quality of life specifically in patients with psoriasis and to validate them and establish the sensitivity of their response to the effects of therapeutic interventions.

The use of objective scales, such as the PASI and the BSA, is essential for assessing disease severity before starting systemic therapy and to facilitate subsequent assessment of response to treatment. These instruments are also essential for correctly assessing treatment response in the context of clinical trials. However, in many cases the results of scales alone are inadequate for defining severity from the standpoint of the patient's needs. The criteria of prior hospitalization, which has been proposed as an indicator of severity, is highly dependent on each country's healthcare system (availability of beds, willingness to be hospitalized, etc) and would not, in general, be a very useful criteria in Spain. In the definition of psoriasis disease severity and the decision to use either conventional or biologic systemic treatment, factors other than the extension and severity of the lesions must be taken into account. Other cases of psoriasis that are considered severe include those involving special forms of the disease known to have a more aggressive course (pustular, erythrodermic, etc), cases that fail to respond to topical treatment, and those in which the disease affects

particular areas of the body (face, hands, flexures, genitalia, etc) and have, therefore, a greater psychological and social impact on the patient irrespective of the PASI score or percent of affected BSA.

Consensus has been reached on an operative definition of moderate to severe psoriasis as that presented by patients who are candidates for phototherapy or systemic therapy.¹⁴

A global disease assessment can be made on the basis of the characteristics of the lesions. There are 2 primary modalities: static and dynamic assessment. In the latter, the physician assesses overall improvement from baseline. Since dynamic assessment is based on the memory of the observer and is difficult to repeat, static Physician's Global Assessment (PGA) has become the standard. The following 6-point scale is generally used for global assessment of psoriasis: 0 = clear; 1 = almost clear, minimal; 2 = mild; 3 = mild to moderate (slight plaque elevation and/or mild infiltration, moderate erythema and/or scaling); 4 = moderate; 5 = moderate to severe (marked plaque elevation, infiltration, erythema, and scaling); and 6 = severe.

Severity of psoriasis can also be defined operatively in terms of the measured or expected response to topical treatment and the need for systemic treatment. Although this decision may be determined in part by subjective factors (on the part of the physician or the patient and essentially related to a desire to avoid possible adverse effects or the need for monitoring), the prescribing doctor can usually foresee the need for systemic treatment on the basis of the past medical history and current disease activity.

Thus, independently of the PASI score, the affected BSA, or the DLQI at any given time, psoriasis in a particular patient can be classified as:

1. Mild psoriasis (grade I): responds to topical treatment.
2. Moderate to severe psoriasis (grade II): requires (or has previously required) systemic treatment (including conventional drugs, biologic agents, and photochemotherapy).

A recent epidemiological study of 3320 patients with moderate to severe psoriasis carried out in Spain and Portugal confirmed that these patients are generally undertreated.⁴ The authors found that one-third of the patients had not received systemic therapy or phototherapy during the 2 years prior to the study. Moreover, although 80% of the patients presented an active relapse of the disease at the start of the study (average affected BSA of 23%, average PASI of 14.3%), a quarter of them were receiving only topical treatment. In a German study, only 45% of the patients with the most severe psoriasis (PASI >20) had ever received systemic treatment.¹⁵

It should be remembered that the "rule of tens" criteria for severity was used in clinical trials in which the participants had not recently received any treatment ("therapeutic wash out"). When none of the therapeutic objectives described below are achieved in a patient receiving systemic treatment, the patient should be considered a candidate for a change of medication or biologic therapy even when the objective scores (BSA, PASI, and DLQI) are lower than those specified above.

Indication for Systemic Treatment

Systemic treatment is indicated in patients with psoriasis in the following situations: a) disease not controlled with topical treatment; b) extensive disease (BSA >5%-10%); c) PASI >10; d) rapid worsening; e) involvement of visible areas; f) functional impairment (palmoplantar or genital involvement); g) subjective perception of severity (DLQI >10); h) extensive erythroderma or pustular psoriasis; and i) disease associated with psoriatic joint disease.

Treatment Objectives

The objective of treatment is satisfactory therapeutic control of psoriasis, and the ultimate goal (ideal outcome) is sustained complete clearance (PGA = 0) or almost complete clearance (PGA = 1) or, when this is not possible, a minimal localized area of affected skin that can be controlled with topical treatment (PGA = 2, PASI <5). With the help of biologic agents, it is now reasonable to expect to achieve this objective in a significant percentage of patients since these new treatments are free from the acute toxicity and cumulative dose-dependent and organ-specific toxicity that makes it difficult to achieve this objective with conventional systemic therapy.

In terms of quality of life, the treatment objective should be to achieve a DLQI of 0 or 1, which indicates that the disease is not affecting the patient's quality of life.^{16,17} The minimum threshold of efficacy required would be a DLQI <5, which indicates that the effect of the disease on the patient's quality of life is slight.¹⁷

In practice, for most patients the treatment objective can be defined in terms of a percentage of relative improvement in PASI after a predetermined interval (for example, 3 or 6 months). With the biologic agents currently available and the new agents still undergoing clinical trials, a reasonable treatment objective should be to achieve a PASI 75 response (within 10 to 16 weeks) and an optimal response would be a PASI 90 response (equivalent to an absence of signs and symptoms, that is, clearance (PGA = 0) or only minimal signs of disease (PGA = 1). This standard would be equally applicable to

conventional systemic treatments with comparable rates of response.¹⁸

A PASI 50 response is considered to be the lowest acceptable threshold of efficacy after 3 months.¹⁶ Physicians should always try to achieve and maintain a PASI 75 response unless the patient considers the response obtained sufficient.

The treatment objective should be one of the following: PASI 75 ($\geq 75\%$ improvement from baseline PASI), PASI <5 , PGA ≤ 1 , or DLQI <5 .

New instruments are needed to assess quality of life, and new studies are required to establish which of the domains of the available instruments (general, dermatological, or psoriasis specific) best reflect changes in response to treatment.

Definition of Treatment Failure

Response to treatment should be assessed continuously during treatment and at 3 to 4 months. Lack of response or treatment failure is defined as follows: a) failure to achieve a 50% reduction in PASI from baseline or loss of such a response; or b) continuing to have a PASI greater than or equal to any of the scores specified above as criteria for moderate to severe psoriasis; or c) any response considered inadequate by both the physician and the patient.

Treatment failure is an indication for changing treatment or prescribing a combination regimen.

Definition of Loss of Response

Loss of response is defined as a failure to fulfill the therapeutic objective at any time during treatment, judged either on the basis of objective parameters (typically failure to sustain the 75% improvement from baseline PASI, that is, the PASI 75 response) or in the opinion of both the patient and the physician.

Loss of response may take the form of a transient exacerbation that can be controlled by adjusting the dosage regimen (dose and frequency of administration) or by prescribing combination therapy (adding topical medication, ultraviolet light B (UV-B) phototherapy, acitretin, methotrexate, or cyclosporine) particularly when the patient is being treated with biologic agents.

Definition of Relapse, Remission, and the Rebound Effect

It is important to establish definitions that allow us to describe the duration of the therapeutic effect of treatment

in the context of both clinical trials and normal clinical practice.¹⁹

Relapse (after withdrawal of effective treatment) is defined as a greater than 50% reduction in the maximal improvement from baseline obtained with treatment (for example, if the PASI was 14 at the start of treatment and 2 when treatment was discontinued, a PASI of 8 or higher would constitute a relapse).

The interval between withdrawal of treatment and relapse is called the period of remission or the duration of therapeutic effect.

The term *rebound effect* refers to either a deterioration of the psoriasis equivalent to at least 125% of the baseline PASI occurring within 3 months of withdrawal of treatment, or a morphological change (the onset of generalized erythrodermic or pustular psoriasis).

Treatment Regimen

The acute or cumulative adverse effects associated with conventional systemic treatment have traditionally led to the use of cyclical regimens and case-by-case selection of medication based on the characteristics and comorbidities of each patient (age, the possibility of conception, alcoholism, obesity, dyslipidemia, hypertension, liver disease, etc). These side effects have also justified the use of rotational therapy, which takes the form of alternating cycles of treatment with different drugs, but in general each patient has an ideal response to a particular drug and some patients have comorbidities or risk factors that limit the range of drugs that can be used. When biologic agents are used, this problem does not exist and the choice of treatment depends principally on the intrinsic characteristics and past history of the disease (need for treatment, etc).

When assessing the indication for biologic treatment in routine practice, a number of factors should be taken into account in addition to the baseline PASI (or alternative assessment using any other severity scale, such as the BSA, PGA, or DLQI). These additional factors include the lack or loss of response to systemic treatment, the patient's intolerance or contraindication to other systemic treatments, as well as the stability or instability of the inflammatory component of the disease (erythema, pain/pruritus) and the rate of deterioration of the current flare. Unstable disease will determine the choice of a treatment known to have a rapid onset of action, whereas stable psoriasis can be treated with a range of different therapies.

Today, the clinician's chief dilemma when prescribing biologic agents is whether to choose continuous (as long as response is sustained) or intermittent (pulse) treatment.

Candidates for Continuous Therapy

1. Patients with a prior history of sustained disease activity involving 1 or more flares during at least 6 months a year in whom treatment has failed to produce a satisfactory level of control or has been curtailed because of contraindications and/or adverse effects.
2. Patients who show a good response to therapy, but who are highly dependent on treatment because of early recurrence (relapses within 2 months or less).
3. Patients in whom loss of response has important psychological repercussions or a significant impact on quality of life.
4. Patients with joint involvement.
5. The presence of comorbidities associated with an increased risk of cardiovascular disease could be a factor to consider in the decision to prescribe continuous treatment.

Biologic agents are the drugs best adapted to a continuous treatment regimen. Owing to their cumulative toxicity, traditional systemic treatments are more suitable for intermittent or rotational treatment regimens.

Candidates for Intermittent Treatment

Patients with a history of exacerbations of short duration with 1 or more flares during less than 6 months a year.

Criteria for Retreatment

Patients who have experienced complete clearance perceive relapse and loss of response quite differently than those who have not experienced clearance for a long time. The negative impact of a particular PASI score on the quality of life and psychological perception of those in the latter group is greater. In such cases, an absolute PASI score above 5, a DLQI of more than 5, or a PGA of at least 3 can be, depending on the case, a reasonable criteria for retreatment.

In the case of a relapse or because of a decision taken jointly by the patient and physician, retreatment with the same agent can be considered or alternatively with a different form of therapy if the circumstance or preferences of the patient have changed.

Transition Between Treatments

Unlike the procedure used in clinical trials (abrupt withdrawal of treatment followed by a washout period), in normal clinical practice the treatment being withdrawn

can be continued throughout a transition period when followed by a biologic agent with a slow onset of response or may be withdrawn abruptly when replaced by a biologic agent with a faster onset of effect, such as infliximab and possibly adalimumab.

When changing a patient's systemic therapy (whether conventional or biologic) because of adverse effects or lack of efficacy, a number of transition strategies can be used depending on the judgment of the physician. These include overlapping the old and new treatments, substitution without continuity, or using an overlapping traditional treatment to cover the transition between 2 biologic regimens.

Combination Therapy

Although combining different therapies is not generally recommended, the combination of topical treatments with biologic agents is often used to increase the rate of response or improve response in the case of localized lesions and to control temporary flare-ups.

Combinations of systemic treatments—including photochemotherapy—with biologic agents can be prescribed (using doses that minimize the risk of side effects) for limited periods of time to prevent a relapse after withdrawal of a systemic treatment, before the onset of the therapeutic effect in the case of certain biologic agents, to accelerate response at the beginning of a course of biologic treatment, to improve therapeutic response to these agents, to control temporary flares, to serve as a transition between biologic treatments, and when treatment is withdrawn because of treatment failure or other causes.

Pretreatment Screening

A complete medical history including the following information should be obtained for all patients with psoriasis who are candidates for systemic treatment: duration of the disease, prior systemic treatments and hospitalizations, presence or absence of arthropathy, history of infectious diseases and possible exposure to tuberculosis, history of past illness, concurrent medications, comorbidities, and the presence of any contraindications or risk factors for adverse effects.

Following a preliminary discussion with the patient concerning the safety, efficacy, and method of administration of the treatment, a quantitative baseline assessment should be performed to determine disease severity (PASI, BSA, PGA, DLQI) and a standard laboratory workup including both complete blood count and biochemistry should be ordered.

Table 1. Contraindications and Possible Adverse Effects of Conventional Systemic Therapy and Photochemotherapy That Must be Taken into Account^a

	<i>Phototherapy</i>	<i>PUVA</i>	<i>Acitretin</i>	<i>Methotrexate</i>	<i>Cyclosporine</i>
Contraindications	Xeroderma pigmentosum, systemic lupus erythematosus, heart failure or ischemic heart disease (orthostatic), claustrophobia	Photosensitivity, squamous cell carcinoma and possibly melanoma, breastfeeding or pregnancy (category C), aphakia, immunosuppression, heart failure or ischemic heart disease (orthostatic), claustrophobia	Pregnancy (category X) , breastfeeding, teratogenicity makes contraception necessary during treatment and for at least 2 to 3 years after treatment Dyslipidemia Liver disease Concomitant treatment with tetracycline	Pregnancy (category X) , breastfeeding , liver disease , alcoholism , immunodeficiency, chronic renal failure	Renal failure, hypertension, neoplastic disease, infections, immunodeficiency, concomitant treatment with PUVA, UV-B, or coal tar Pregnancy (category C) or breastfeeding
Principal toxic effects	Burns, presumed increased risk of skin cancer, premature skin aging	Burns, premature skin aging, increased risk of melanoma and non-melanoma skin cancer, possible eye damage	Fetal death and/or abnormalities, hepatotoxicity	Fetal death and/or abnormalities, myelosuppression, hepatotoxicity, pneumonitis, stomatitis	Nephrotoxicity, hypertension, immunosuppression (increased risk of infection and neoplastic processes)
Other common adverse effects		Nausea	Hair loss, dry lips, cheilitis, dry or sticky skin, hyperlipidemia	Nausea, anorexia, fatigue, headache, hair loss	Hypertrichosis, gingival enlargement, gastrointestinal intolerance, neurological abnormalities, abnormal lipid profile, hyperglycemia, hyperuricemia, hyperpotassemia hypomagnesemia
Other considerations	Availability, logistics, distance from place of residence	Availability, logistics, distance from place of residence. Do not exceed 150-200 sessions	Possible musculoskeletal toxicity	Hypersensitivity hypoalbuminemia, drug interactions. Do not exceed 2-4 g	Drug interactions Avoid overdosing in obese patients (dose in accordance with ideal weight) Do not exceed 1-2 years of treatment

Abbreviations: PUVA, psoralen + ultraviolet A treatment; UV-B, ultraviolet B phototherapy.

^aAdapted from Menter and Griffiths.²⁰ The points that are typically the most important are highlighted in bold face.

1. When considering the prescription of conventional systemic treatment or photochemotherapy, the contraindications and possible side effects shown in Table 1 should be taken into account.²⁰ When considering the prescription of conventional systemic treatment, physicians may also decide to order the following tests: antinuclear antibodies, chest radiograph, Mantoux test with 2 tuberculin units (TU) of purified

protein derivative (PPD)-23, and blood tests for human immunodeficiency virus, hepatitis B and C virus.

2. When treatment with a biologic agent is being considered, the medical history obtained should include the following information: duration of the disease, prior systemic treatments and hospitalizations, presence or absence of arthropathy, history of infectious diseases and possible exposure to tuberculosis, the

presence of comorbidities and possible risk factors for side effects and/or contraindications, history of past illness (with particular emphasis on congestive heart failure, lupus erythematosus, and demyelinating disease, including any possible family history), and concurrent medication.

To rule out latent tuberculosis infection, a chest radiograph and a TB-focused medical history including all the pertinent questions should be obtained. If treatment with a tumor necrosis factor (TNF) α inhibitor is contemplated, a tuberculin skin test should be performed with 2 TU of PPD-23. When the skin test result is negative, the test should be repeated between 7 and 15 days later (to eliminate any confusion due to a booster effect). This two-step testing is particularly important in patients who could be anergic, such as those over 65 years of age and patients receiving treatment with methotrexate, cyclosporine, or other immunosuppressants. The tuberculin skin test is considered positive when the diameter of the induration is at least 5 mm at 72 hours. Even when they do not have radiographic abnormalities, patients with a positive skin test result should follow a course of prophylactic chemotherapy with isoniazid 300 mg/d. While it is generally recommended that chemoprophylaxis should be started 1 month before start of treatment with anti-TNF agents, the minimum necessary interval is unknown and a shorter interval is probably sufficient or it may even be enough to start both treatments simultaneously.²¹ The prophylaxis should be taken for the full 9 months (unless another regimen is used in line with local practice). Alternatively, these patients may be candidates for treatment with efalizumab.

Selection of Conventional Systemic Treatment

In addition to the contraindications, side effects, interactions, and special precautions regarding use

described above, all of which influence the choice of drug, clinicians should also take into account the efficacy-related information summarized in Table 2.^{18,22-25}

Indication for Biologic Treatment

Biologic agents are indicated for the treatment of moderate to severe psoriasis (as defined above) in adult patients who have failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including phototherapy, photochemotherapy, or other biologic agents. Intolerance may be due to side effects or toxicity, whether acute or due to the cumulative dose.

This definition includes the following patients:

1. Patients in whom effective control is not achieved with the available systemic agents, in monotherapy or combination regimens.
2. Patients in whom relapses occur rapidly, that is, less than 3 months after withdrawal of any type of treatment.
3. Patients who require high doses of conventional systemic therapies (with the risk that entails of adverse effects due to acute or cumulative toxicity in a substantial percentage of patients).
4. Patients who are intolerant to some systemic therapies (who experience toxicity or adverse reactions with effective doses) or have a high risk of cumulative toxicity with methotrexate, cyclosporine, acitretin, or photochemotherapy even when laboratory test results are normal. The risk of toxicity may be due to the dose required, the duration of treatment, individual susceptibility, or to individual risk factors, such as age, sex, comorbidity, and potential drug interactions.
5. Patients who are not good candidates for treatment with photochemotherapy because of their work, daily schedule, travel requirements, or availability.

The efficacy data available from the clinical trials does not allow us to differentiate between patients in

Table 2. Efficacy-Related Information for Traditional Systemic Treatments

	<i>Acitretin</i>	<i>Methotrexate</i>	<i>Cyclosporine</i>
Standard dose regimen	0.3-0.5 mg/kg for 4 weeks, subsequent increase	5-20 mg/wk	2.5-4 mg/kg (maximum 5 mg/kg)
Onset of clinical effect usually occurs within:	4-8 weeks	4-8 weeks	4 weeks
Efficacy: PASI 75 at 8-16 weeks	Highly variable and difficult to establish: 25%-56%	25%-60%	50%-70%
Efficacy: PASI 90 or clearance at 8-16 weeks	9%	11%	13%-50%

Adapted from references 18, and 22 to 25.

Table 3. Efficacy-Related Information for Biologic Agents^{18,25-33}

	<i>Efalizumab</i>	<i>Etanercept</i>	<i>Etanercept</i>	<i>Etanercept</i>	<i>Infliximab</i>	<i>Adalimumab</i>
Dose Regimens	0.7 mg/kg sc 1st dose, 1 mg/kg weekly	25 mg sc twice weekly 24 weeks	50 mg sc twice weekly 12 weeks, then 25 mg twice weekly until 24 weeks	50 mg sc once a week 24 weeks	5 mg/kg iv induction 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
Efficacy: PASI 75 at 10-16 weeks	22%-39%, 12 weeks	30%-34%, 12 weeks	49%, 12 weeks	38%, 12 weeks	80%, 10 weeks	71%-80%, 16 weeks
Efficacy: PASI 75 at 24 weeks	44%	44%-56%	54%	71%	82%	70%
Efficacy: PASI 90 at 10-16 weeks	No data	11%-12%, 12 weeks	21%-22%, 12 weeks	14%, 12 weeks	57%, 10 weeks	45%-51%, 16 weeks
Efficacy: PASI 90 at 24 weeks	No data	20%-21%	No data	42%	58%	49%
Duration of remission, (median) ²⁹	84 days	70-90 days		No data	140 days after induction	No data
Long-term treatment	Response sustained	Response sustained; studies with different doses (50 mg/wk, 50 mg twice weekly)		No data available	61% PASI 75; 45% PASI 90; at week 50	87% PASI 75; 63% PASI 90; at 18 months
Most commonly reported adverse effects	Flu-like symptoms, high white blood cell and lymphocyte counts	Injection site reactions			Infusion reactions	Injection site reactions
Chief risks ^a	Exacerbation or rebound of psoriasis, thrombocytopenia	Tuberculosis and other infections			Tuberculosis and other infections	Tuberculosis and other infections

^aGuidelines have recently been published on the subject of treatment monitoring and the use of vaccinations in patients treated with biologics for psoriasis.³⁴

Abbreviations: iv, intravenous; sc, subcutaneous.

Adapted from references 18 and 25 to 33.

whom biologic therapy is indicated because of a lack of response to conventional systemic therapy and those who are candidates because they are intolerant to or have contraindications to the doses of conventional systemic treatment required to achieve a satisfactory response. These 2 subgroups of patients may have different therapeutic needs, and these needs might even determine the choice of biologic agent.

All the biologic agents approved for the treatment of psoriasis must be made available to all patients who are candidates for such therapy, without unnecessary delay or any type of limitation representing inequitable treatment.

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.

Selection of Biologic Therapy

As well as any potential contraindications, side effects, and special precautions for use discussed above that determine the choice of drug, the efficacy-related information shown in Table 3 should also be taken into account.^{18,25-33}

None of the biologic agents should be considered generally preferable to the others in the treatment of moderate to severe psoriasis on the basis solely of response rates published in clinical trials. Instead, the choice of a biologic agent should be made on a case-by-case basis for each patient taking into account the available information and recommendations.

The choice of biologic treatment should be made in each case taking into account the following considerations:

1. Patient-related factors, such as the presence of concomitant disease, psoriatic arthropathy, comorbidity, weight, and the risk of possible adverse effects.
2. The disease characteristics including the following:
 - a) the case history (prior treatment, speed of relapse after treatment, whether disease activity is intermittent or continuous); and b) the situation of the psoriasis at the time of prescribing, that is, current disease activity (PASI), intensity of inflammation, and rate of deterioration (instability).
3. The patient's preferences regarding the dosage regimen and the efficacy and safety profile of the drug.

Final Note

The prescribing physician should carefully read the instructions in the EMEA Summary of Product Characteristics and compare them with the recommendations in this consensus statement, particularly with regard to dose, contraindications, and possible interactions.

Conflict of Interest

L. Puig, X. Bordas, J.M. Carrascosa, E. Daudén, C. Ferrándiz, J.M. Hernanz, J.L. López Estebanz, J.C. Moreno, J.L. Sánchez Carazo, F. Vanaclocha, and H. Vázquez Veiga have received sponsorship from Abbott, MerckSerono, Novartis, Schering-Plough, and Wyeth for participation in clinical trials, and to attend or speak at meetings.

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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.

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

The First Article in The Journal *Actas Dermo-Sifiliográficas* Published With Photographs: Malignant Keratosis Diffusa Fetalis (Fetal Ichthyosis; Congenital Maligna Keratoma, Etc.), by Juan de Azúa

Actas Dermosifiliográficas. 1909;1:77-90.

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Hiperkeratosis universal congénita maligna. (Ictiosis fetal; keratoma maligno congénito, etc.).

POR JUAN DE AZÚA.

El caso que presento, pertenece á una especie morbosa, mal conocida y delimitada, que ha recibido múltiples nombres. Su aspecto, semejante á la *Ictiosis*, y la predominancia en ella de alteraciones de cornificación, han servido para denominarla *Ictiosis congénita*, *Ictiosis fetal congénita*, *Ictiosis fetal ó intra-uterina*, *Ictiosis sebácea*, *Keratosis congénita*, *Keratoma difuso congénito*, *Keratoma maligno difuso congénito*, *Keratoma maligno congénito*, *Hiperkeratosis universal difusa congénita*, *Hiperkeratosis fetal*, *Hiperepidermotrofia generalizada y Eritrodermia congénita ictiosiforme con hiperepidermotrofia*, siendo también conocida por el aspecto raramente monstruoso de sus casos más intensos, con el nombre de *feto tarlequin*.

Año 1.

Julio 1909.

Núm. 2.

ACTAS DERMO-SIFILIOGRÁFICAS

SUMARIO. — OYARZÁBAL: Chancro sifilítico forunculoide del pubis ó inoculación sobre un forúnculo de un chancro sifilítico. — Vacuna en el dorso de las manos. — ALVAREZ SÁINZ DE AJA: Dos casos de síndrome de GUILLAIN-THAON. — J. S. COVISA: Un caso de pénfigo vulgar. — NONELL: Un caso de sifiloma uretral perforante precoz. — J. DE AZÚA: Hiperkeratosis universal congénita maligna. — Prúrigo en placas simétricas de origen probablemente tuberculoso. — Intoxicaciones mercuriales terapéuticas. — Preparación de los calomelanos, salicilato de mercurio, etcétera, según la fórmula de LANG. — Contagiosidad de la lepra. — Procedimiento del émbolo anestésico para los lavados uretro-vesicales por presión.

Abstract. Brief comment is made on the first article published in the journal *Actas Dermo-Sifiliográficas* with photographic documentation of the case history and histological findings. It was written by the founder of the journal, Dr. Juan de Azúa, in 1909.

Key words: *Actas*, Azúa, photography, history

EL PRIMER ARTÍCULO CON FOTOGRAFÍAS DE LA REVISTA ACTAS DERMO-SIFILIOGRÁFICAS: HIPERKERATOSIS UNIVERSAL CONGÉNITA MALIGNA. (ICTIOSIS FETAL; KERATOMA MALIGNO CONGÉNITO, ETC.), POR JUAN DE AZÚA

Resumen Se realiza un breve comentario del primer artículo publicado en la revista *Actas Dermo-Sifiliográficas* con documentación gráfica del caso clínico y de los hallazgos histológicos. Fue redactado por nuestro fundador, el Dr. Juan de Azúa, en el año 1909.

Palabras clave: *Actas*, Azúa, fotografía, historia

The first *Actas Dermo-Sifiliográficas* article in which photographs appear was the piece published by Azúa in 1909 entitled “Generalized malignant congenital hyperkeratosis (fetal ichthyosis; malignant congenital keratoma, etc.).”¹

Azúa describes a case “of a morbid, little known, and infrequent type that has been named in a variety of ways.”

Subsequently, he stresses his interest in this patient, since “because severe cases usually result in death after the first hours or days of life, they are observed mainly by midwives, and it is rare for a dermatologist to be able to study them.”

Azúa was called in by a famous obstetrician at the Madrid maternity hospital, Dr Enrique de Isla, in May

1909, to “examine a child with a serious skin disorder, born that same day and not likely to survive long.” The patient, in fact, died that same afternoon, 10 hours after birth and a half hour before Azúa arrived at the maternity hospital.

Dr. Azúa takes note of the basic information: the mother was young and strong, not suffering from syphilis, and without skin disorders. The pregnancy and delivery were normal. The fetus was female, of average length and weight, born with respiratory distress and weak sucking reflex.

His description of his examination of the deceased infant is worth transcribing word for word: “The body was still warm. On it I observed, mainly in the folds of the joints, genital organs, neck, scalp, and ears a sebaceous coating, not very thick and dirty white in color, consisting of dead epidermal cells and fat, as subsequently confirmed. The entire skin surface was hard and stiff, resistant, inflexible: the horny layer resembled leather split in several places by long, deep, bloody cracks. These cracks formed radial patterns around the anus, vulva and mouth that recalled the fissures typical in cases of hereditary syphilis. The ears, with rudimentary and malformed auricles barely separate from the head, had a narrow auditory canal clogged with epidermal detritus. The extremely blunt nose had very small nostrils. The mouth was circular, and between its cracked, stiff, and immobile lips a fairly well-formed tongue appeared. The eyes were obscured by eyelid ectropion and could not be seen. Herniated conjunctivae appearing between the everted eyelids formed red protuberances... The vulva was open and flat, with small fissures around the vaginal orifice. There was not the slightest trace of hair, eyelashes or eyebrows.

On the hands and feet, the fingers and toes were cylindrical in shape and thin, the nail plate covered in a horny casing that obscured the nails...” (Figure 1). Figure



Figure 1. Case history