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OPINION ARTICLE

Commentary on European and British Guidelines for the Treatment of Psoriasis

Comentarios a las directrices europeas y británicas sobre el tratamiento de la psoriasis

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The European S3 guidelines on the systemic treatment of psoriasis[1] and the British Association of Dermatologists' guidelines for biologic interventions for psoriasis[2] were published shortly after the Spanish guidelines, whose coauthors included the authors of this article.[3] Without entering into an exhaustive discussion of the transcription or even conceptual errors that may be found in any publication, the importance of these guidelines is such that they merit a critical review and general commentary for the benefit of readers of *Actas Dermo-sifiliográficas* and dermatologists treating patients with psoriasis.

Introduction

The purpose of evidence-based guidelines is to improve patient care, bearing in mind drug efficacy, safety, and effectiveness data, and patient preferences and satisfaction. Guidelines provide ground rules for choosing and monitoring treatments and have the ultimate aim of improving the quality of care.[4] Although there are specific instruments for evaluating the quality of such publications, such as the Appraisal of Guidelines Research and Evaluation,[4] the success of guidelines is ultimately determined by user satisfaction and improvement in the standard of care for patients.

The preparation of evidence-based guidelines for the treatment of a disease represents the culmination of a process in which available scientific evidence is assessed and critically reviewed so that recommendations can be based on the strength of that evidence. This process is based on searches in databases such as PubMed, EMBASE, Cochrane, DARE, etc, followed by an exhaustive review of original studies and clinical trials, an evaluation of systematic reviews and meta-analyses of original studies and trials, and a comparison of any published summaries and synopses.

Evidence-based guidelines, governed as they are by a rigorous methodology, are crucial in terms of providing physicians with a summary review of the issues that affect the decision to use one treatment or another. However, they are no substitute for clinical judgment and case-by-case prescription, given that the patient's interests must be placed above all other considerations.

The legal basis for treatment is the prescribing information for a product; however, standard medical practice—which has both medical and legal implications—may be based on guidelines. Evidence-based guidelines are also frequently referred to when deciding on payment or reimbursement of treatment costs, or when health care authorities and insurance bodies place restrictions on prescriptions. For ethical reasons, however, freedom of prescription must prevail because the ultimate priority is the welfare of individual patients.

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The recently published European and British guidelines have certain limitations and shortcomings that we discuss below.

Representativeness (European S3 Guidelines)

Although the publication of country-specific guidelines—such as those for The Netherlands,[5] Britain,[2,6] Germany,[7] and Spain[3]—is fully justified by the great differences in health care systems and prescription practices in Europe, and even among regional authorities within countries, the European guidelines, based as they are on the experience of a wide range of experts, are undoubtedly useful for the development of more local guidelines. The European guidelines were developed, in a project launched some years ago by the European Dermatology Forum under the auspices of the European Academy of Dermatology and Venereology, by a committee with 23 members and a subcommittee with 39 members. However, only one Spaniard sat on the guidelines committee and no Spanish dermatology expert was invited to participate. Even in the final drafting stage, the suggestions of those of us who had kindly been invited to look over the manuscript shortly before publication were not taken into account.

Efficacy

The fact that the European guidelines only consider the induction phase of treatment (10-16 weeks) makes sense, given that this phase is the primary concern of the clinical trials that provide the evidence base. After the induction phase, double blinding generally ends and an open-label treatment phase commences, in which placebo-treated patients go on to receive the active agent while the other patients continue with the same treatment.

The different rates at which treatments reach the efficacy plateau is an important factor to be considered when rapid onset of action is required; however, for many patients and physicians, outcome should be evaluated after approximately 6 months.

Variability in the study endpoint, when the primary outcome is evaluated, has important implications for efficiency studies,[8] given that drug costs are determined by the time interval between treatments, which tends to vary. The ideal period after which to evaluate the efficacy of a treatment is probably around 1 year. The patient's weight and response to the treatment should also be taken into account, as well as whether treatment is continuous or intermittent.

Whenever possible, guidelines should include whatever information is available on the effect over the medium (24-26 weeks) and long (52-100 weeks) term, and also on withdrawal effects (time to recurrence), re-treatment, and when appropriate, possible adjustments to dosage aimed at optimizing the therapeutic response.

A 75% or better improvement over baseline in the Psoriasis Area and Severity Index (PASI 75) is considered to be the standard goal for a clinically significant improvement in psoriasis in both clinical trials[9] and routine clinical practice.[10] Possibly more relevant for the patient, however, is a 'clear' or 'almost clear' Physician Global Assessment (PGA) response (0-1), or the achievement of a PASI 90 response (a 90% or better improvement over baseline). These values, when available, are not always included in the treatment recommendations given in the published guidelines.

The selection of a 'cut-off point' or threshold for the primary efficacy outcome measure (percentage of patients achieving a PASI 75 response in the short term) is always arbitrary (why 60%, and not 50% or 70%?). A more important methodological shortcoming is the failure to take the placebo effect into account in clinical trials. For this reason, as with meta-analyses,[11-13] information on incremental efficacy or relative (RR), or probability of achieving the predefined outcome with the intervention with respect to placebo and number needed to treat (NNT) should be provided, whether for PASI 75, PASI 90, or whatever other therapeutic outcome measure or goal is established.

Although a qualitative scale could be used (eg, based on using crosses, arrows, etc) to simplify the presentation of results for efficacy (or safety) in the guidelines, numeric data should also be provided, leaving it to the prescribing physician to make the decision regarding his/her own cut-off point. For example, a prescribing physician could use the data in the Table to select his/her desired threshold for achieving a PASI 75 response (but why not PASI 90?)—based on response probability (50%, 70%, 80%, etc), RR (10, 15, 18, etc), or NNT (1, 2, etc)—thus including one, two or three available tumor necrosis factor (TNF) antagonists among his/her preferable therapeutic options on the basis of incremental efficacy. However, this does not imply that treatment with any other of the biologics should always be ruled out, or that a drug lower down in the list may not benefit a specific patient more. A graphic representation of RR or response probability for a specific efficacy goal is very useful in terms of providing a rapid overview of the relative efficacy of different treatments. An example for response probability is given in the Figure, based on the same meta-analysis[13] and on studies of particular drugs.[14,15]

A biologic cannot be selected a priori on the basis of a patient's baseline PASI. Rather, when making an individualized treatment decision, the drug should be selected taking into account the clinician's (and patient's) desire of a more rapid onset of action, a greater response rate, or a weight-adapted dose.

Given that prescription results from a decision-making process based on the multiple attributes of a particular drug, patient, and disease, value judgments ('recommended, suggested', etc) are of dubious value in terms of establishing a specific rank or preference for prescribing. The ultimate decision should be made on a case-by-case basis, and should take into account not only the efficacy of the therapeutic intervention in comparison with a placebo or other interventions, but also possible adverse effects, the interests of the patient, the route of administration, patient-related factors (weight, the presence of arthritis and concomitant diseases, contraindications and special precautions, lack or loss of response, possible treatment interruption because of journeys, pregnancy, surgery,

Table Scientific Evidence Available for Systemic Treatments for Psoriasis. Summarized Results of a Meta-analysis[a]

	PASI 50	PASI 75	PASI 90
Response probability (95%CI)			
Placebo	14 (12-16)	4 (4-5)	1 (1-1)
Etanercept: 50 mg twice a wk	74 (67-80)	50 (43-58)	22 (17-28)
Infliximab: 5 mg/kg	93 (91-96)	81 (75-86)	54 (47-63)
Methotrexate: 15-22.5 mg once a wk	66 (51-77)	42 (27-54)	17 (9-26)
Ciclosporin: 3 mg/kg/d	57 (37-73)	33 (17-49)	11 (4-21)
Adalimumab: 40 mg once a fortnight	88 (83-93)	71 (63-79)	42 (33-52)
Relative risk (95%CI)			
Placebo	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Etanercept: 50 mg twice a wk	5.28 (4.58-6.02)	11.73 (9.40-14.29)	34.74 (24.77-46.68)
Infliximab: 5 mg/kg	6.68 (5.90-7.55)	18.93 (15.98-22.52)	84.51 (65.17-109.8)
Methotrexate: 15-22.5 mg once a wk	4.74 (3.52-5.73)	9.76 (6.08-13.19)	25.99 (12.41-41.38)
Ciclosporin: 3 mg/kg/d	4.06 (2.54-5.31)	7.62 (3.65-11.65)	17.87 (5.86-33.74)
Adalimumab: 40 mg once a fortnight	6.33 (5.52-7.16)	16.71 (13.57-20.1)	65.61 (47.49-87.79)
Number needed to treat (95%CI)			
Etanercept: 50 mg twice a wk	2 (1.52-1.86)	2 (1.88-2.59)	5 (3.62-6.10)
Infliximab: 5 mg/kg	1 (1.22-1.31)	1 (1.22-1.40)	2 (1.60-12.17)
Methotrexate: 15-22.5 mg once a wk	2 (1.58-2.69)	3 (1.99-4.35)	7 (4.00-12.66)
Ciclosporin: 3 mg/kg/d	2 (1.70-4.45)	4 (2.26-8.26)	11 (4.87-29.11)
Adalimumab: 40 mg once a fortnight	1 (1.27-1.45)	1 (1.34-1.71)	2 (1.96-3.11)

[a]Adapted from Bansback et al.[13]

A reader can select the cutoff point and criterion for efficacy that seems to suggest the most suitable recommendation, even though specific guidelines may orient the reader by providing a measure of the strength of the recommendation (for example, a PASI 75 response probability over 60% or a PASI 90 response probability over 20%, or relative risk of more than 10 or 50, respectively, or a need to treat 2 patients or fewer for the corresponding efficacy measures).

Abbreviations: CI, confidence interval; PASI, Psoriasis Area and Severity Index.

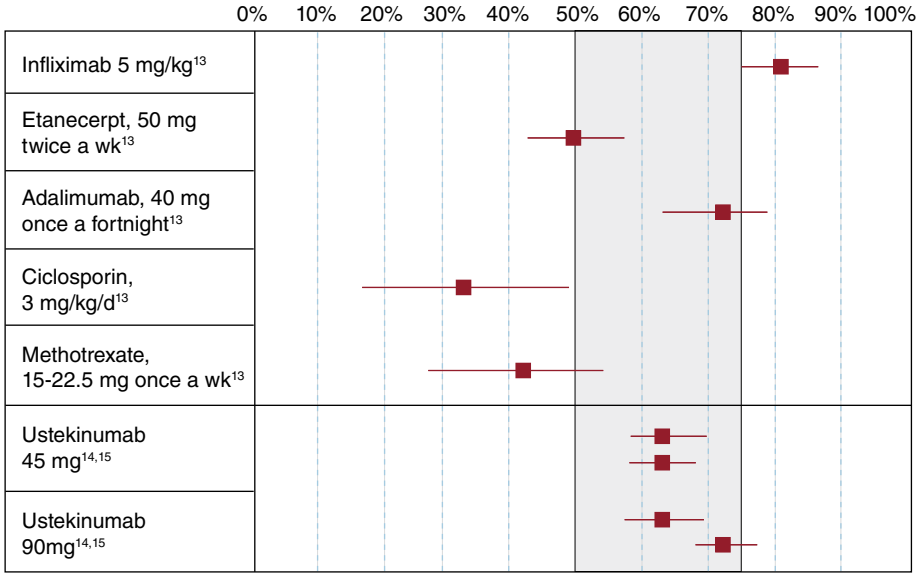

Figure Graph of the probability (95% confidence interval) of obtaining a Psoriasis Area and Severity Index (PASI) improvement of 75% or more (PASI 75) after induction treatment (10-16 weeks) using a number of systemic and biologic treatments[13-15] for moderate to severe plaque psoriasis. Any point in the shaded area (probability of obtaining a PASI response of 50%-75%) could be considered valid as a recommendation for guidelines on therapy. However, the availability of increasingly active drugs (in terms of the percentage of patients achieving the pre-established therapeutic goal, maximum PASI improvement, and rapid onset of action) has led dermatologists and patients to become more demanding regarding the expected efficacy of a treatment.

etc), and flare-up characteristics (rebound, spreading, or inflammation requiring a rapid response). These particular situations are not generally taken into account in recruiting patients for clinical trials, even though they often determine the efficacy and safety profile of the drug administered to individual patients.

Safety

Guidelines commonly confuse contraindications with warnings and precautions in the prescribing information. For example, although it is not recommended to administer anti-TNF agents to patients with severe heart failure (classes III and IV of the New York Heart Association), this should not be considered an absolute contraindication in the case of etanercept. Nor should pregnancy necessarily be considered an absolute contraindication for anti-TNF agents. The Food and Drug Administration (FDA) pregnancy category B indicates that animal studies have failed to demonstrate a risk to the fetus and there are no adequate or well-controlled studies in pregnant women, or alternatively, in the case that animal studies have shown an adverse effect, adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. (This last alternative is, in fact, unlikely, given that the demonstration of adverse effects in animal experiments would preclude the implementation of studies in humans). There is minimal transplacental passage of immunoglobulin G molecules in the critical first trimester,[2] and, on this basis, the recommendation regarding monoclonal antibodies should be to suspend treatment once it is known that a patient is pregnant, so as to avoid transplacental passage of the monoclonal antibodies from the second trimester onward.[16]

The recommendations for preventing tuberculosis reactivation are also contentious, in terms of treatment regimen (which clearly depends on the situation in each country), and also in terms of the recommended treatment interval before initiating biologic treatment (2 months based on level-4 evidence[2]), given that there is as yet no consensus among experts regarding this interval (normal practice is 1 month, but there is no evidence against reducing the waiting period when the severity of the psoriasis would strongly indicate a need to commence treatment).

Implicit and Explicit Costs and Therapeutic Recommendations

The British guidelines[2,6] have made recommendations based not only on scientific evidence but on pharmacoeconomic or strictly budgetary criteria. These are not, perhaps, issues that properly belong in guidelines. Although physicians do have a social responsibility to contain costs and ensure that available resources are used efficiently, they also have an ethical commitment to their patients, and effectively act as guardians who ensure that their patients receive the best possible treatment. For this reason, we consider it to be unacceptable and arbitrary to enforce a 6-month waiting period for biologic treatment for patients with severe psoriasis,[6] and applaud the fact that this requirement has been removed from the current edition of the British guidelines.[2] We also consider it unacceptable to recommend using infliximab only when rapid onset of action is necessary, or for patients with variants of pustular or erythrodermic psoriasis[6] which are not listed in the prescribing information and were not considered as inclusion criteria in the corresponding clinical trials.

In clinical trials, most patients have had moderate to severe psoriasis (PASI >10-12), and there is no published evidence that the response of patients with more severe psoriasis (PASI >20) is better or worse; therefore, there is no reason whatsoever to reserve infliximab (or any other biologic) for the treatment of this subpopulation.[17] The implicit reasoning behind reserving biologics with a greater response probability (based on clinical trials) for use in patients with more severe psoriasis or as a third-line of treatment is not supported by any scientific evidence.

This bias has been removed from the latest edition of the British guidelines,[2] and there is implied acknowledgment of the lack of scientific evidence on approving infliximab for use only in patients with PASI >20; in contrast, the recommendation of the National Institute for Health and Clinical Excellence (NICE), attached to the National Health Service for England and Wales, is to use infliximab only for severe cases of psoriasis. No significant differences have been demonstrated regarding the response to infliximab based on baseline PASI (PASI 75 response of 70.9% compared to 2.3% for placebo in patients with baseline PASI <20; PASI 75 response of 76% compared to 1.3% for placebo in patients with baseline PASI ≥20) or the nature or number of previous treatments.[18] Nonetheless, dubious recommendations continue to be made, such as that of relegating ustekinumab to the role of a rescue medication for cases where there is no response to TNF-blocking agents (how many?). This recommendation has no scientific basis, nor is any justification given (other than a lack of information on safety and the possible convenience of going along with practices for other specialities). Although ustekinumab has recently been included in the British guidelines as a treatment for patients with previous experience of biologic treatment, there is no justification for relegating it to the role of rescue medication. Nor is the relative lack of experience regarding its safety any justification, as clinical trials performed with ustekinumab in patients with psoriasis have included more patients/year in follow-up than trials performed with other biologics. The results of recent trials, including analyses of subpopulations of patients with previous exposure to various systemics or biologics, confirm the efficacy of ustekinumab in these patients, although efficacy is slightly lower than in biologics-naive patients.

The available data does not indicate the best way to manage a lack or loss of response to treatment with TNF antagonists. Undoubtedly, factors such as patient weight should be taken into account in treatments based on fixed doses, and also biologic immunogenicity and clearance.

When faced with a situation where the efficacy of a TNF-blocking biologic is inadequate or null, a great deal of experience and clinical judgment is required to decide whether to use another agent (which one?) from the same group, or to switch to ustekinumab. This decision also needs to be made on a case-by-case basis and not by automatically following the recommendations of guidelines.

A shortcoming of both the European and British guidelines is the uncritical acceptance of the restriction imposed on the prescription of biologics—their indication as a second-line treatment—in the prescribing information of the European Medicines Agency (EMEA). The British guidelines indicate that the strength of the recommendation is D and the level of evidence is 3,[2] whereas the European guidelines do not report any evidence level for this restriction.

Restrictions on this treatment indication, apart from considerations of psoriasis severity, are exclusively attributable to cost-control concerns. There is nothing in the inclusion criteria or the results of clinical trials approved by US or European regulatory bodies that indicate that only patients who fail to respond to other treatments, or with intolerance to, or contradicted for, systemic treatments—including ciclosporin, methotrexate or psoralen plus ultraviolet A light)—should be considered candidates for biologic treatment. Based on the available evidence, the FDA has approved a number of biologics for the treatment of moderate to severe psoriasis, without imposing the restrictions regarding previous treatment that are included in the EMEA's prescribing information. Physicians concerned for their patients' wellbeing must act according to the prescribing information for legal reasons (except in cases of compassionate use); they also need to ensure that the authorities will subsidize the treatment. However, although they may take note of the restriction, they do not have to take it at face value, given that it is not based on any scientific evidence.

Therapeutic decisions should be made on a case-by-case basis in the context of medical care tailored to each patient. The notion that treatments are interchangeable (implying that a physician should always select the treatment offering the greatest probability of achieving a specific response) is the mistaken premise of decision makers not in direct contact with routine medical practice. The response of an individual patient at a specific moment in time cannot be predicted from the results of clinical trials conducted with groups of patients with very different characteristics from those observed in clinical practice; a PASI 75 response, for example, may represent an excellent or totally inadequate response for a particular patient, depending on his/her personal circumstances.

Although financial and pharmacoeconomic considerations may be specified in guidelines as an important decision-making criterion, and might determine possible restrictions on reimbursement for treatment in a health care system, they should not form part of the therapeutic decision as such.

The NICE guidelines[19] are simply prescription recommendations that provide a framework for justifying reimbursement decisions in a specific health care context. With a view to minimizing costs, they take efficiency into account rather than the maximum benefit of the individual patient. Complying with an efficiency goal—even if praiseworthy in terms of enabling more patients to receive specific treatments in a context of limited resources—is likely to affect optimal care.

In general terms, the response to biologic treatments is better when the dose is adapted to the patient's weight. To enhance treatment efficiency, and, at the same time, minimize weight-related cost differences, reimbursement policies can be adapted to each health care setting.[20] Another alternative is to only reimburse efficacious treatments (with efficacy defined, for example, as achieving a PASI[75] response or PGA score of 2 or less within 12-16 weeks and thereafter sustaining it). Patient associations and groups of experts from national dermatology associations should play an important consultative role and should even participate in decision making regarding efficacy and effectiveness. Such measures would ensure fairer and more efficient resource allocation, and would optimize treatment based not only on the scientific evidence available (which only provides short-term data on the populations included in clinical trials), but also on individual patient response.

Conflicts of Interest

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