5 European S3-Guidelines on the Systemic Treatment of Psoriasis Vulgaris

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List of abbreviations

AGREE	Appraisal of Guidelines Research & Evaluation
ADR	Adverse drug reaction
BBUVB	Broadband UVB
BIW	Biweekly
BSA	Body Surface Area
BW	Body weight
CSA	Ciclosporin
dEBM	Division of Evidence-Based Medicine
DLQI	Dermatology Life Quality Index
EADV	European Academy of Dermatology and Venereology
EDF	European Dermatology Forum
EOW	Every other week
GE	Grade of evidence
IM	Intramuscular
IPC	International Psoriasis Council
ITT	Intention-to-treat
IV	Intravenous
MED	Minimal erythema dose
MOP	Methoxypsoralen
MPD	Minimal phototoxic dose
MTX	Methotrexate
NBUVB	Narrowband UVB
NYHA	New York Heart Association
PASI	Psoriasis Area and Severity Index
PASI 50/75/10	50/75/100 per cent improvement from baseline PASI
PDI	Psoriasis Disability Index
PGA	Physician´s Global Assessment
sPGA	Static Physician's Global Assessment
SC	Subcutaneous
TL01	UVB 311 nm

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5.1 Introduction to the guidelines

5.1.1 Needs analysis/problems in patient care

Pathirana/Nast/Rzany

Psoriasis vulgaris is a common dermatologic disease, with an incidence in Western industrialized countries of 1.5% to 2% [1]. In more than 90% of cases the disease is chronic [1].

Patients with psoriasis vulgaris have significantly impaired quality of life. Depending on its severity, the disease can lead to a substantial burden in terms of disability or psychosocial stigmatization [2]. Indeed, patient surveys have shown that the impairment in quality of life experienced by patients with psoriasis vulgaris is comparable to that seen in patients with type 2 diabetes or chronic respiratory disease [3].

Patients are often dissatisfied with current therapeutic approaches, and their compliance is poor. Patient surveys have shown that only about 25% of psoriasis patients are completely satisfied with the success of their treatment, while over 50% indicate moderate satisfaction and 20% slight satisfaction [4]. The rate of non-compliance with systemic therapy is particularly high, ranging up to 40% [5]. In addition to limited efficacy and poor tolerance, explanations for these figures include fear and a lack of information among patients regarding adverse events (e.g. due to perceived poor communication between patients and physicians).

Frequently, in settings where high-level (i.e. evidence-based) guidelines are lacking, therapeutic strategies are not based on evidence. Moreover, there are major regional differences in the use of the various therapeutic approaches. Experience has shown that the choice of treatment for patients with psoriasis vulgaris is often made according to traditional concepts, without taking into consideration the detailed, evidence-based knowledge currently available regarding the efficacy of individual treatment options. In addition, physicians are frequently hesitant to administer systemic therapies, both because of the added effort involved in monitoring patients for adverse events and, in some cases, due to the risks of multiple interactions with other drugs [6].

5.1.2 Goals of the guidelines/goals of treatment

Mrowietz/Reich

Treatment goals in psoriasis

Guidelines for the treatment of psoriasis provide an overview of a variety of practical aspects relevant to selecting drugs and monitoring patients on therapy [7–11]. Based on the evaluation of efficacy and safety data, as well as on the practical experience obtained with different treatment modalities, they contain a range of recommendations reached in a structured consensus process.

Epidemiological studies conducted in Germany and other countries, as well as the results of patient surveys in Europe and the United States, have indicated that mean disease activity in patients with psoriasis is high and quality of life is

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poor, even among patients who are seen regularly by dermatologists; moreover, these findings are accompanied by data showing low treatment satisfaction and a demand for more efficacious, safe, and practical therapies [12–15].

Although there are no generally accepted treatment goals in psoriasis patients at present, a number of concepts have emerged from the ongoing discussion. These, together with the present guidelines, may help dermatologists decide when and how to progress along existing treatment algorithms, ultimately improving patient care. These concepts are based on a selected list of outcome measures that take into account not only the severity of skin symptoms but also the impact of disease on health-related quality of life (HRQoL).

Although it has its drawbacks, the most established parameter to measure the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI), which was first introduced in 1978 as an outcome measure in a retinoid trial [16]. The PASI is also part of most currently used classifications of disease severity in psoriasis [17] and represents a necessary first step in selecting a treatment strategy. In recent clinical trials, especially those investigating biological therapies, the most commonly used primary efficacy measure has been the PASI 75 response, i.e. the percentage of patients who at a given point in time achieve a reduction of at least 75% in their baseline PASI. Because this parameter (or an equivalent response criterion) is reported in many trials on systemic therapies for psoriasis, and because a PASI 75 response is now widely accepted as a clinically meaningful improvement, it also serves as the central evidence-based efficacy parameter in these and other psoriasis treatment guidelines. It should also be noted that a PASI 75 response, as is documented in these guidelines, can be achieved in the majority of patients with the therapeutic armamentarium presently available for the treatment of moderate to severe disease. Therefore, although the complete clearance of skin lesions may be regarded as the ultimate treatment goal for psoriasis, a PASI 75 response has been proposed as a treatment goal that is both practical and realistic [18]. Based on the data available from clinical trials, this goal should be assessed between 10 and 16 weeks after the initiation of treatment, i.e. the time during which PASI responses were typically evaluated as the primary outcome measure (Table 5.1). There is evidence that some patients may reach a PASI 75 response at a later time (i.e. between 16 and 24 weeks of therapy), especially when treated with drugs such as methotrexate, the fumaric acid esters, etanercept, or efalizumab*.

HRQoL is an important aspect of psoriasis, not only in defining disease severity but also as an outcome measure in clinical trials. The Dermatology Life Quality Index (DLQI) is the most commonly used score for assessing the impact of psoriasis on HRQoL. It consists of a questionnaire with 10 questions related to symptoms and feelings, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment [19]. The DLQI is assessed as a score ranging from 0 to 30, and the meaning of the absolute DLQI has been categorized and validated into bands [20]. These bands describe the overall impact of skin disease on a person's HRQoL as follows: 0–1 = "no effect"; 2–5 = "small effect"; 6–10 = "moderate effect"; 11–20 = "very large effect"; 21–30 = "extremely large effect." Another study demonstrated that a change of five points

* "The European Medicines Evaluation Agency (EMEA) has recommended the suspension of the marketing authorization for Efalizumab, as announced by Arzneimittelkommission der Deutschen Ärzteschaft: http://www.akdae.de/20/10/2009-055.html, visited on March 18, 2009, 19:58h."

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in the DLQI correlates with the minimum clinically meaningful change in a person's HRQoL [21]. Although there is no correlation between absolute PASI and absolute DLQI scores [12], there seems to be a correlation between an improvement in PASI and an improvement in the DLQI. The drugs that produce the highest PASI reduction by the end of induction therapy are also associated with the greatest reduction in DLQI [22]. A DLQI of 0 or 1 has been proposed as a treatment goal [18] and indicates that the HRQoL of the patient is no longer affected by psoriasis (Table 5.1).

In daily practice, it may be useful to define a second set of treatment goals that serve as "lowest hurdles" (i.e. a minimum of efficacy that should be achieved). If these goals are not met, a treatment should be regarded as inefficient and must consequently be stopped and replaced by another treatment option. A PASI 50 response and DLQI <5 have been proposed as a potentially useful minimum efficacy goal. [18]. Treatment goals should be monitored at appropriate intervals during long-term maintenance therapy (e.g. at 8-week intervals).

Additional treatment goals may be required in individual patients, such as those with joint or nail involvement or with other psoriasis-related comorbidities.

Table 5.1 Proposal for treatment goals in psoriasis (adapted from [18])

	Skin symptoms	HRQoL
Treatment goals (assessment after 10 to 16 weeks, and every 8 weeks thereafter)	PASI 75 or, alternatively, PGA of "clear" or "almost clear"	DLQI of 0 or 1
Minimum efficiency; "lowest hurdle"	PASI 50	DLQI <5 or, alternatively, DLQI improvement of at least 5 points

5.1.3 Notes on the use of these guidelines

Pathirana/Nast/Rzany

These guidelines are intended for dermatologists in the clinic and in private practice, as well as for other medical specialists involved in the treatment of psoriasis vulgaris. Furthermore, they are meant to serve as an aid for health insurance organizations and political decision-makers.

Discussions of the different therapeutic approaches have been deliberately restricted to aspects that the experts felt were especially relevant. Steps that can be considered part of every physician's general obligations when prescribing drugs (e.g. inquiring about allergies and intolerance reactions, as well as identifying potential contraindications) are not listed individually. Furthermore, all patients should be informed about the specific risks associated with any given systemic therapy.

Readers must carefully check the information in these guidelines and determine whether the recommendations contained therein (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, and up to date. The authors and publishers can take no responsibility for dosage or treatment decisions taken in this rapidly changing field. All physicians following the recommendations contained in these guidelines do so at their own risk. The

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authors and the publishers kindly request that readers inform them of any inaccuracies they may find.
As with all fields of scientific inquiry, medicine is subject to continual development, and existing treatments are always changing. Great care was taken while developing these guidelines to ensure that they would reflect the most current scientific knowledge at the time of their completion. Readers are nevertheless advised to keep themselves abreast of new data and developments subsequent to the publication of the guidelines.

5.1.4 Methodology

Spuls/Ormerod/Smith/Saiag/Pathirana/Nast/Rzany

A detailed description of the methodology employed in developing the guidelines can be found in the methods report.

Base of the guidelines

The three existing evidence-based national guidelines (GB, NL, DE) for the treatment of psoriasis vulgaris were compared and evaluated by a group of methodologists using the standard internationally Appraisal of Guidelines Research and Evaluation (AGREE) instrument. The group decided that all three guidelines fulfilled enough criteria to be used as the base for the new evidence-based European guidelines on psoriasis [23].

Database and literature search

The literature evaluated in the existing national guidelines serves as the basis for the present set of European guidelines. In cases where the national guidelines differed in terms of the grade of evidence they assigned to a particular study, this study was re-evaluated by the above-mentioned group of methodologists. For the systemic interventions covered by the national guidelines, and for novel systemic interventions, a new literature search, encompassing studies published between May 2005 and August 2006, was conducted using MEDLINE, EMBASE, and the Cochrane Library. To ensure a realistic evaluation of the biologics covered in these guidelines, an additional search was performed for these interventions, with an end date of 16 October 2007. Altogether, searches were performed for the following systemic interventions: methotrexate, ciclosporin, retinoids, fumaric acid esters, adalimumab, infliximab, etanercept, alefacept, and efalizumab. Combination therapy was not included in the search.

Evaluation of the literature

The evaluation of the literature focused on the efficacy of the different interventions in the treatment of plaque psoriasis. After a preliminary review of the literature, each study identified as potentially relevant was appraised by one methodologist using a standardized literature evaluation form (LEF). A second appraisal was conducted by a member of the dEBM. If the two appraisals differed, the study was reassessed. A total of 678 studies were evaluated, 114 of which fulfilled the criteria for inclusion in the guidelines. Studies were included if they

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fulfilled the methodological quality criteria specified on the literature evaluation form (for details see appendix LEF and the Guidelines Methodology Report). Studies that did not meet these criteria were excluded.
Other aspects of the interventions (e.g. safety and combination therapy) were evaluated by the participating experts based on their many years of clinical experience and in accordance with the publications available, but without conducting a complete, systematic review of the literature.

Evidence assessment

To asses the methodological quality of each study included for efficacy analysis, a grade of evidence was assigned using the following criteria:

Grades of evidence

A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A2; the results of the different studies included in the meta-analysis must be consistent
A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size)
B Randomized clinical study of lesser quality, or other comparable study (e.g. nonrandomized cohort or case-control study)
C Non-comparative study
D Expert opinion

In addition, the following levels of evidence were used to provide an overall rating of the available efficacy and safety data for the different treatment options:

Levels of evidence

1 Studies assigned a grade of evidence of A1, or studies that have predominantly consistent results and were assigned a grade of evidence of A2.
2 Studies assigned a grade of evidence of A2, or studies that have predominantly consistent results and were assigned a grade of evidence of B.
3 Studies assigned a grade of evidence of B, or studies that have predominantly consistent results and were assigned a grade of evidence of C.
4 Little or no systematic empirical evidence; extracts and information from the consensus conference or from other published guidelines.

Therapeutic recommendations

For each intervention, a therapeutic recommendation was made based on the available evidence and other relevant factors. The recommendations are presented in text form, rather than using scores or symbols (e.g. arrows) to highlight the strength of the recommendation. For the statements on efficacy, the following scale was agreed upon, based on the PASI results of the included studies for each intervention:

PASI 75 >60%: intervention recommended
PASI 75 30–60%: intervention suggested
PASI 75 <30%: intervention not suggested

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