VII. Disease severity and treatment goals

i. Measuring disease severity

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 [1].

Health related quality of life (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 ten questions related to symptoms, mental health, impact on daily life , leisure, work and school, personal relationships and burden psoriasis treatment [2].

ii. Defining disease severity

The first European consensus effort to define treatment goals for moderate-to-severe psoriasis was conducted in 2011 [3]. According to the consensus, the definition of moderate-to-severe disease was '(PASI > 10 or body surface area [BSA] > 10) AND DLQI > 10', and for mild psoriasis 'PASI ≤ 10 AND BSA ≤ 10 AND DLQI ≤ 10'. Criteria to further "upgrade" mild disease to moderate-to-severe where defined as: major involvement of visible areas, major involvement of the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques.

The DLQI describes 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". A change of five points in the DLQI has been shown to correlate with the minimum clinically meaningful change in a person's HRQoL [4]. Although there is no correlation or only weak correlation between absolute PASI and absolute DLQI scores [5], there seems to be a correlation between an improvement in PASI and an improvement in the DLQI [6].

Since the European consensus, the discussion about defining disease severity has evolved further.

The International Psoriasis Council (IPC) ran a modified Delphi consensus process among its counsellors to categorize psoriasis severity and to redefine access criteria to systemic therapy. The most preferred statement from the IPC survey "rejects the mild, moderate, and severe categories in favour of a

dichotomous definition: Psoriasis patients should be classified as either candidates for topical therapy or candidates for systemic therapy; the latter are patients who meet at least one of the following criteria: (1) body surface area >10%, (2) disease involving special areas, and (3) failure of topical therapy". [7]

The severity definition that reached the second highest approval rate did provide a dichotomous distinction: "a) mild or mild to moderate: that which can be adequately controlled with topical therapy alone; b) moderate to severe or severe: that which requires phototherapy or systemic therapy (including biologics)". [7]

A definition using precise numbers got only moderate support from the IPC counsellors, defining mild as BSA 0%-5% with special areas not affected and with DLQI <5, defining moderate as BSA 5%-10% or special areas affected; or BSA 1%-5% and DLQI 5-10, and defining severe as >10% BSA or special areas affected; or BSA 5%-10% and DLQI >10. [7]

A physician global assessment (PGA) score to evaluate disease severity can be beneficial for the everyday clinician in order to rapidly assess the severity of psoriasis. It is important to note that different PGAs exist and may differ in the way they are defined. A PGA score of 3 or more is commonly used in clinical trials in order to define a moderate-to-severe form of psoriasis and an indication for systemic treatment. PGA 0/1 is also used both in clinical trials as well as in the everyday clinical practice as a definition of treatment success. [8-10]

National societies are invited to define and use their own national disease severity grading in line with their local conditions. .

iii. Treatment goals

The 2011 European Consensus on Treatment Goals

The European Consensus Programme defined treatment goals for the first time for psoriasis [3]:

In accordance with concepts of uncontrolled disease and the commonly used definition of treatment failure, an algorithm had been generated that can be used in daily practice to secure effective treatment (Figure 1). Treatment success was defined as an improvement of 75% or more in PASI. Treatment failure was defined as not achieving a PASI of 50. Reaching an improvement of more than 50% but less than 75% but achieving a DLQI score of equal to or lower than 5 was considered treatment success whereas a DLQI score above 5 was considered treatment failure.

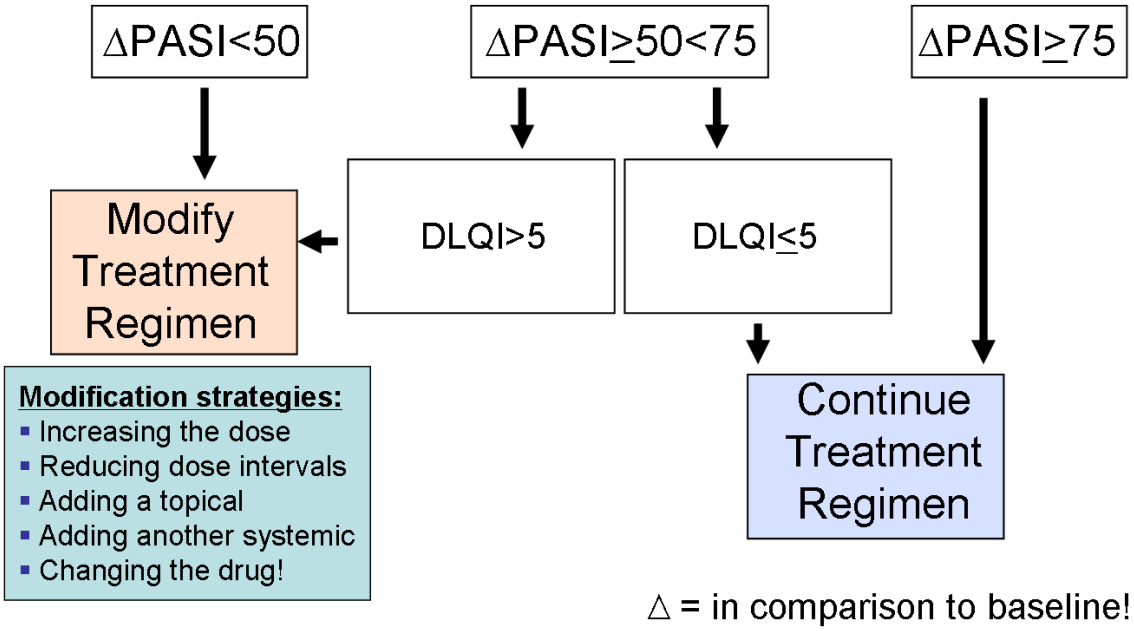

Figure 1: Treatment goal algorithm from the 2011 "European Consensus Programme" (modified from Mrowietz et al. 2011) [3]

A first point in time to assess treatment success for fast acting drugs (e. g., CsA, infliximab) should start at the end of induction therapy up until 16 weeks after the initiation of treatment. For drugs with a slower onset of activity (e. g., MTX, fumarates [FUM], etanercept), treatment assessment should begin at the end of induction therapy up until 24 weeks after starting therapy. During maintenance treatment, an assessment of treatment success should be made in intervals in accordance with the safety monitoring recommendations (typically every eight to twelve weeks).

An important consideration when utilizing treatment goals is the demand for action in case the goal is not met. In psoriasis there are a number of measures that can be applied to increase efficacy such as increasing the dose, reducing the time between applications, or adding another drug (combination therapy); however, with certain drugs this may represent off-label therapy as such variations are not backed-up by the summary of product characteristics (SmPC). When dose adjustments are either ineffective or not appropriate, changing the drug is an important step. As there is little evidence on how to shift from one drug to another, a global consensus programme provided guidance based on a combination of evidence from the literature and on expert opinion [11].

Advancements after the European Consensus on Treatment Goals

Since the European consensus group process, more treatment options for psoriasis have become available and considerable progress has been made. Because of these advancements, higher treatment goals (e.g. PASI 90 or PASI 100) are aimed for [12].

In addition, the focus has shifted away from percentage reduction and towards a targeted final outcome (e.g. PASI <= 2, DLQI < 2 or PGA clear or almost clear) [10,13].

National societies are invited to define and use their own national disease severity grading in line with their local condition.

Time till onset of action

Psoriasis can have a severe impact on an individual's health related quality of life. The time until the onset of action of different treatments for psoriasis has been found to vary between the different treatment options [14]. Although psoriasis is a chronic skin disease, rapid clearance has been identified as a crucial outcome for patients [14]. Taking the time necessary for 25% or 50% of patients to achieve a given PASI or ACR (modified American Rheumatology criteria) response, available systematic reviews summarize the evidence on the speed of onset of action of the different drugs [15-17]. Estimates of what is acceptable for a patient as 'waiting time' until a treatment becomes effective, vary largely from patient to patient. Looking at the proportion of patients dropping out of clinical trials due to a lack of efficacy as a proxy, a strong increase in the rate of dropouts was seen after 10-12 weeks [18]. Sequential combination of slow acting drugs with low response rates carries a risk of long patient 'waiting times', until a noticeable, clinically meaningful improvement in their health related quality of life [19].

References

1. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238-44.
2. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clinical and experimental dermatology* 1994; **19**: 210-6.
3. Mrowietz U, Kragballe K, Reich K *et al.* Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Archives of dermatological research* 2011; **303**: 1-10.
4. Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *The British journal of dermatology* 2002; **147 Suppl 62**: 50.
5. Augustin M, Kruger K, Radtke MA, Schwippl I, Reich K. Disease severity, quality of life and health care in plaque-type psoriasis: a multicenter cross-sectional study in Germany. *Dermatology* 2008; **216**: 366-72.

6. Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. *The British journal of dermatology* 2007; **156**: 945-50.
7. Strober B, Ryan C, van de Kerkhof P *et al.* Recategorization of psoriasis severity: Delphi consensus from the International Psoriasis Council. *J Am Acad Dermatol* 2020; **82**: 117-22.
8. Dauden E, Puig L, Ferrandiz C, Sanchez-Carazo JL, Hernanz-Hermosa JM. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis: Psoriasis Group of the Spanish Academy of Dermatology and Venereology. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2016; **30 Suppl 2**: 1-18.
9. Nast A, Gisondi P, Ormerod AD *et al.* European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2015; **29**: 2277-94.
10. Nast A, Spuls PI, van der Kraaij G *et al.* European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2017; **31**: 1951-63.
11. Mrowietz U, de Jong EM, Kragballe K *et al.* A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2014; **28**: 438-53.
12. Torres T, Puig L. Treatment goals for psoriasis: Should PASI 90 become the standard of care? *Actas dermo-sifiliograficas* 2015; **106**: 155-7.
13. Mahil SK, Wilson N, Dand N *et al.* Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR). *The British journal of dermatology* 2020; **182**: 1158-66.
14. Seston EM, Ashcroft DM, Griffiths CEM. Balancing the Benefits and Risks of Drug Treatment: A Stated-Preference, Discrete Choice Experiment With Patients With Psoriasis. *Archives of dermatology* 2007; **143**: 1175-9.
15. Egeberg A, Andersen YMF, Halling-Overgaard AS *et al.* Systematic review on rapidity of onset of action for interleukin-17 and interleukin-23 inhibitors for psoriasis. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2020; **34**: 39-46.
16. Nast A, Sporbeck B, Rosumeck S *et al.* Which antipsoriatic drug has the fastest onset of action? Systematic review on the rapidity of the onset of action. *The Journal of investigative dermatology* 2013; **133**: 1963-70.
17. Pham PA, Dressler C, Eisert L, Nast A, Werner RN. Time until onset of action when treating psoriatic arthritis: meta-analysis and novel approach of generating confidence intervals. *Rheumatol Int* 2019; **39**: 605-18.
18. Nast A, Dilleen M, Liyanage W, Aikman L, Szczypa P, Dressler C. Time, Psoriasis Area and Severity Index and Dermatology Life Quality Index of patients with psoriasis who drop out of clinical trials on etanercept because of lack of efficacy: a pooled analysis from 10 clinical trials. *The British journal of dermatology* 2018; **178**: 400-5.
19. Zidane M, Dressler C, Gaskins M, Nast A. Decision-Analytic Modeling for Time-Effectiveness of the Sequence of Induction Treatments for Moderate to Severe Plaque Psoriasis. *JAMA dermatology* 2019.