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Psoriasis: to treat or to manage?

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Abstract: The recognition of psoriasis as a systemic disorder with characteristic skin symptoms and associated diseases has changed treatment concepts substantially. The complexity of psoriasis disease not only requires appropriate therapy but also weight-loss and smoking cessation programmes as well as trigger factor elimination. The term 'management' may better reflect the aim for a holistic approach of disease control. Comorbidity and the presence of psoriatic arthritis are important denominators for drug selection. However, there is a lack of prospective data substantiating a benefit of associated diseases by antipsoriatic therapy. Securing success using treatment goals helps to establish an efficacious therapy and to control inflammation. A regular scoring of disease severity, patients' quality of life and assessment of other clinically relevant conditions are mandatory to closely follow the disease course. There is debate whether an early treatment may modulate the future course of psoriasis. Concepts of minimal disease activity have not been implemented in psoriasis yet. There is a lack of evidence how long any treatment should be given and when and how to terminate. Finally, outcome tools should specifically be tailored for psoriasis to evaluate disease-related items as well as the benefit of management from the patient's perspective.

Key words: biologics – comorbidity – management – psoriasis – treatment

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Introduction

What is the real profession of a physician? It is to treat diseases and to take care of patients. It is quite simple if a fractured bone has to be fixed: a clear diagnosis and a concept on how to mechanically stabilize the fragments can be made. However, even in this situation, there may be the choice whether to use a cast or surgical intervention and in case of surgery which technique/material may be best. But there is no doubt that a fractured bone needs appropriate treatment.

Does psoriasis as a 'benign' condition always need treatment and can the condition be seen as 'fractured skin'? It is an ongoing discussion why, when and how to treat inflammatory dermatoses, while there is no such discussion in, for example, skin cancer.

With the availability of modern treatment options for inflammatory skin disorders namely biological agents, there is a constant request to justify their use in non-malignant diseases (1). Today, prescription of the new and cost-intense biological agents registered for chronic immune-mediated inflammatory diseases including rheumatoid arthritis (RA), ankylosing spondylitis, inflammatory bowel disease (IBD) and psoriasis/psoriatic arthritis is accompanied with the question of a patient's benefit (2).

Although the definition of patient's benefit is a multidimensional approach, there seems to be a different understanding in oncology as compared to inflammation medicine.

In oncology, measuring survival and/or survival with a good quality of life can easily assess a benefit from treatment. Such outcome assessments are much more difficult to make in chronic inflammatory conditions, but attempts have been made to close this gap (3).

One of the first concepts highlighting the demand for successful treatment achieving a measurable medical and patient's benefit was put forward in rheumatology. The most important aspect of this concept is its preventive nature. The 'treat-to-target' regimen in RA was based on the fact that RA can be destructive leading to irreversible damage of joints that result in physical disability with all subsequent consequences for patient and society (4). Logically, the aim of any intervention is to stop the destructive disease progress. It has convincingly been shown that in RA, there is a phase within the early disease course where such intervention has the highest likelihood to be preventive in freezing the disease in a state with only minimal residual damage, and this phase has been termed 'window of opportunity'. Missing this window increases the chance for disease progression and subsequent organ destruction that cannot be reverted at later disease stages (5).

One parameter to follow the course of RA is radiographic progression together with clinical scores (6). In IBD, this concept has somewhat been adapted and is communicated as 'mucosal healing' (7).

Another important concept with major implications for management is 'minimal disease activity (MDA)'. In RA, MDA is defined as 'a state which is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations'. (8) Meanwhile, the MDA concept was adapted to PsA and successfully tested in a recent trial (9,10). However, in psoriasis, the MDA approach has not been established yet.

What differentiates psoriasis from RA and IBD? When focusing solely on the skin lesions, the major difference is that even from severely inflamed and longstanding lesions, no residual tissue damage results on the level of the naked eye view and conventional histology after resolution. Plaques with major induration, erythema and scaling or pustular lesions in which the inflammatory process is maximal revert to clinically and structurally normal skin after appropriate therapy or even spontaneously. Of course,

the situation in psoriatic arthritis differs completely and is very similar to RA.

Interesting new data from molecular biology has shown that up-regulated genes persist in lesional psoriatic skin after the lesions were cleared by using a tumor necrosis factor alpha (TNFα)-antagonist (11). Such genes have been termed remnant genes and may reflect the fact that either there is underlying pathology in uninvolved skin of patients with psoriasis (under genetic control?) or molecular residual damage. Both scenarios may explain induction of lesions by trigger factors, and the fact that at least in some patients, there is a quick relapse of disease after cessation of therapies.

The story of comorbidity

Already in 1995, it became clear that psoriasis is associated with other non-dermatological diseases, and by today, this is commonly referred to as psoriasis comorbidity (12,13). The major implication of psoriasis being associated with other diseases is the new and now widely accepted concept of psoriasis as a systemic inflammatory disease (14).

Metabolic syndrome has been identified as a very important associated condition because of a subsequent or parallel development of atherosclerosis that is the background of complications such as myocardial infarction and stroke (15,16).

In fact, patients with psoriasis have a decreased life expectancy of up to 5 years resulting from cardiovascular complications (17,18). Meanwhile, it has been substantiated that depression and anxiety disorders are also associated with psoriasis and may occur already in paediatric patients with psoriasis (19,20).

The most important comorbidity of psoriasis is obesity (21,22). Investigations over the last years have shown that a BMI (body mass index) >30 doubles the risk of getting psoriasis and obesity is an independent risk factor for the disease across different ethnic groups (23). Smoking has also been shown in a number of cohort studies to be an independent risk factor for psoriasis (24–26).

Treating the skin or the patient?

Clearly, psoriasis is a disease that requires adequate therapy. The current treatment paradigm is to clear or substantially reduce lesions reverting the pathologic skin changes back to normal. It has been nicely demonstrated that life-limiting conditions such as myocardial infarction in patients with psoriasis are dependent on the severity of skin symptoms (27). In a Danish nationwide cohort study, the risk of atrial fibrillation and ischaemic stroke was already enhanced in patients with mild psoriasis and increased with severity of the disease in comparison with the Danish population (28). These data may allow a 'risk stratification' within the psoriasis patient population identifying patients, for example, with moderate-to-severe psoriasis to be at risk with the consequence to apply systemic therapy (29,30).

Psoriasis is the first dermatological inflammatory disorder where the goal is to manage skin lesions and associated diseases. Taking into account their importance for the patients' general health, this approach is justified by the need to cover the many spheres of psoriasis disease (Fig. 1). An attempt to include the different levels of psoriasis into a risk assessment is the 'cumulative life course impairment' (31,32). For the transition of these new concepts into care, the term 'management' may better reflect this ambition.

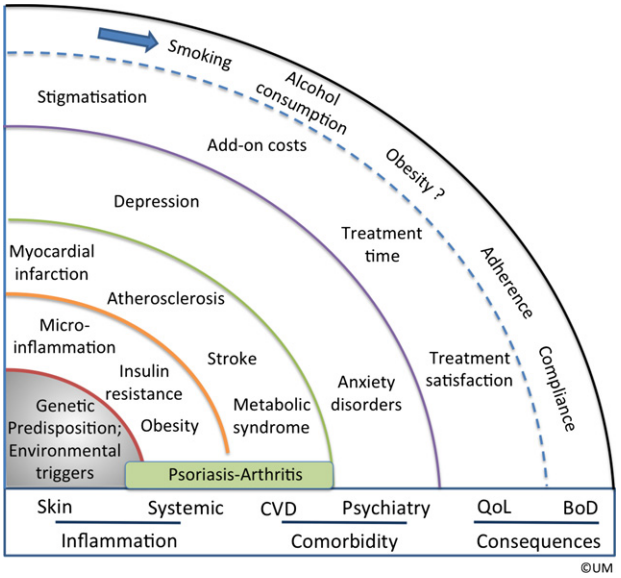

Figure 1. The spheres of psoriasis disease. CVD, cardiovascular disease; QoL, quality of life; BoD, burden of disease.

The different levels of psoriasis management

Effective therapy and treatment goals

Scoring of psoriasis allows for a definition of severity and is essential for qualified care. The most recent one was established during a European consensus programme (29). In this programme, apart from body surface area (BSA) and psoriasis area and severity index (PASI), a patient-related quality-of-life questionnaire (dermatology life quality index, DLQI) was used. According to the European consensus, mild psoriasis was defined as BSA<10 and PASI<10 and DLQI<10 and moderate to severe as (BSA>10 or PASI>10) and DLQI>10. There was agreement that mild psoriasis should preferentially be treated with topical therapy, and in case of inadequate response, UV light should be added. In case of moderate-to-severe psoriasis, systemic therapy should be initiated.

Effective therapy of psoriasis skin lesions is the most important requirement of any management concept. Ideally, the applied regimen completely clears the lesions. To achieve this result, quality control measures need to be established. An important step to include quality controls in psoriasis management is the definition of treatment goals. However, there was (and still is) debate on how to define 'effective' therapy.

According to the European consensus programme (29), not achieving an improvement of PASI of 50% (PASI50) is defined as treatment failure or inadequate response. An effective therapy was defined as achieving a reduction of PASI of 75% (PASI75) or more. In the range between PASI50 and 75, the dermatology life quality index (DLQI) is used to decide whether or not the treatment goals have been met. These outcome parameters have meanwhile been implemented in national guidelines such as in Australia (33) and Germany (30).

The most important consideration of establishing treatment goals in medicine – that also applies for treatment goals in psoriasis – is the demand for action in case the goal is not met. In psoriasis, this means adjustment of treatment either by increase of

dose or, if feasible decrease of dosing intervals, starting combination therapy or, in the end changing of the drug. To provide some guidance for treatment transitioning, a global consensus programme aimed to discuss real-life scenarios (34).

Treatment according to severity

About two decades ago, the treatment paradigm was escalation and rotation. Patients with psoriasis even presenting with moderate-to-severe disease as to today's definition were first treated with topicals, and in case of failure, UV light was added. Only if such combinations were not sufficient, patients were started on a systemic therapy. After achieving improvement or clearance therapy was stopped and only re-started when there was a relapse.

By today, the treatment concept has changed completely. The arguments for this change came from different angles. A major driver was the fact that psoriasis is now perceived as a systemic disorder with skin manifestation and associated diseases that are responsible for increased morbidity and mortality. At the same time, a number of new drugs allowing long-term use became available namely the TNFα antagonists and the IL-12/IL-23p40 antibody ustekinumab. Supportive of the change was the requirement for new drugs to be explored in long-term studies that enable to assess not only efficacy but also safety on the long run (35,36).

Adjusting dose and intervals

In most of the drugs, the label also states dosing of the compound and the application frequency. However, in particular, during long-term maintenance therapy, dose adjustments are required from a medical perspective. This may either be an increase in the dose and/or reduction in the dosing intervals in case of partial therapeutic response or the prolongation of the dose intervals or the reduction in the dose after achieving clearance of lesions. In principle, such dose adjustment strategies are logical consequences of the therapeutic outcome, but several issues argue against such an approach. A major issue is the fact that most of the dose adjustments are not backed-up by the label and the SmPC (summary of product characteristics) and therefore represent off-label use. In addition, there are some drug-related issues that need to be kept in mind before deciding to vary dose and/or interval.

The issue of antidrug antibodies in biological therapy

Biological agents registered for the treatment of moderate-to-severe psoriasis in most countries are the monoclonal antibodies against TNFα adalimumab and infliximab and against IL-12/IL-23p40 ustekinumab as well as the fusion protein etanercept, a TNFα receptor construct. Regardless of the nature of the therapeutic antibody (fully human, humanized or chimeric), they represent neo-antigens for the patient's immune system. Indeed, a surprisingly high proportion of patients treated for RA, psoriatic arthritis or psoriasis with the fully human antibody adalimumab or the chimeric construct infliximab develop antibodies, which are named antidrug antibodies (ADA).

In the case of ustekinumab, ADAs have been reported in up to 5.5% of treated patients, but there is no report about a causative role for secondary non-response. Different constructs such as the fusion protein etanercept or the pegylated Fab-fragment certolizumab-pegol registered for RA and psoriatic arthritis seem to be less immunogenic in comparison with full monoclonal antibodies (37).

The presence of ADA can have many different effects of which two have been best substantiated. First, ADA can decrease the therapeutic efficacy leading to secondary non-response if they are of neutralizing nature, and second, as in case with infliximab cause infusion reactions. The first effect may also lead to decreased trough drug levels (37,38).

In principle, ADA can be detected by immunoassays; however, their value is under debate for various reasons. One is that sensitivity and specificity are insufficient to reliably monitor ADA in clinical routine and another that only very few laboratories provide such expensive assays. To get valuable insight whether or not ADA may impair the therapeutic response determination of drug blood levels in parallel to ADA is essential (39).

The consequences of a possible development of ADA are important for any variation in dose and/or interval. As with vaccinations, a prolongation of dosing intervals may lead to a boostering effect for ADA development (40).

There is conclusive literature evidence that cotreatment with drugs such as methotrexate even in a low-dose regimen (5–10 mg/week) is able to inhibit ADA generation in a clinically meaningful fashion (41). Interestingly, in case of already existing ADA during treatment with infliximab, the addition of methotrexate may be able to restore clinical efficacy and further prevent infusion reactions; however, there is very few literature addressing this approach (42). Apart from prolongation of dose intervals, reduction of the dose may also lead to an increase of ADA (43).

Which systemic drug for which patient?

There is no data or a consented algorithm available which drug to choose when a patient with psoriasis qualifies for systemic therapy. On the basis of prescription information, there is considerable difference in different countries although international and local guidelines do not provide a ranking of drug use. Obviously, the first, second and third choice within the group of conventional drugs is made by personal preferences, availability and reimbursement status/price. The same situation applies for the group of biological agents. In some countries, healthcare authorities determine which biological agent has to be given first before the other can be considered (44).

Although there is published information about all registered compounds that is easily accessible through web-based sources, there is still considerable lack of knowledge about the different drugs registered for psoriasis therapy in the general dermatological community. In a recent survey to detect possible barriers for the use of biological therapy for psoriasis among 300 dermatologists in 5 European countries and Canada, it became clear that the high price of biologics is a major barrier for their use apart from medical reasons (45).

The decision of a dermatologist to choose/favour a drug is a complex interplay of knowledge and own experience that is influenced by communication with experts in the field. The observation of adverse events in treated patients will lead to a negative attitude even if such events are known to be rare. On the contrary, a series of patients presenting with a clinical response above the level of expectation will likely result in a positive attitude.

Due to a lack of clear evidence/data, it is very difficult by today to include possible effects of drugs on associated diseases into drug selection algorithms. Prospective studies with outcomes measures for such conditions are needed for such purpose.

For biological agents, we propose an algorithm based on the additional presence of psoriatic arthritis or highly active psoriasis in which a fast and sufficient control of disease is needed. As shown in Fig. S1, in patients with psoriasis skin manifestation only, a first choice biological could be ustekinumab, and in patients with skin manifestations with concomitant psoriatic arthritis, the anti-TNF antibodies adalimumab or infliximab may be used first. Because of its limited and slower onset of efficacy, etanercept is second choice. In patients with very active, severe plaque psoriasis, infliximab is most efficacious with a fast onset of efficacy. Its application is physician controlled, which is an important aspect to ensure safety and drug adherence.

For conventional therapy, such discrimination is more difficult. Acitretin and fumarates do not have an established and significant effect on psoriatic arthritis and even methotrexate is ineffective in psoriatic arthritis presenting with enthesitis, dactylitis, spinal involvement or sacroiliitis (46).

For ciclosporine being the most efficacious of the conventional drugs in plaque psoriasis, the current guidelines do not recommend long-term therapy because of possible structural kidney damage and an increased risk of non-melanoma skin cancer in patients treated with UV light (47). Although methotrexate is widely used mainly because it is a very cheap drug, data clearly link possible hepatotoxicity to the simultaneous presence of diabetes and/or obesity both of which are known associated diseases in psoriasis (48,49).

Early treatment philosophy

As mentioned above, rheumatologists have proven the concept of early treatment within the 'window of opportunity'. The aim of this concept is to prevent progression of disease, which by today also includes comorbidity.

Is there any evidence that by treating psoriasis early after first diagnosis regardless of severity the lifetime course can be changed? No data are available to either substantiate or disapprove such approach.

An interesting aspect would be to include outcomes of associated diseases in such scenario. There is already debate whether effective therapy can prevent cardiovascular mortality mainly myocardial infarction and stroke. First data generated in retrospective cohort studies provide evidence that appropriate therapy can significantly decrease the risk of myocardial infarction (50).

The concept of the 'psoriatic march' provides arguments for an early treatment concept; however, until today, there is no proof that the stepwise disease progression is indeed dependent on previous events and not the result of a genetic predisposition together with environmental factors (51). And there is no hint indicating a 'window of opportunity' within the 'march'. In fact, data from studies in childhood psoriasis convincingly show that important associated diseases including metabolic syndrome are already present in children with psoriasis and obviously do not develop after psoriasis manifestation (52,53). Whether early psoriasis therapy in patients with potential risk factors, namely obesity and/or metabolic syndrome at the time of first diagnosis, can prevent subsequent major cardiovascular events is completely unknown by today.

Treatment forever?

There is agreement that severe psoriasis requires effective therapy to control the disease. Treatment needs to be continued as long as required. In clinical practice, during maintenance therapy, two main scenarios exist: (i) re-occurrence of (minimal) psoriasis before the next dosing and/or no complete clearance of lesions while on treatment and (ii) full clearance and no signs of deterioration at any timepoint while on treatment. Whereas the argument to continue therapy in the first group seems obvious, there is understandable debate if and when to stop in the second scenario.

There are no data or evidence published to assist the clinician in this difficult situation that is complicated by the paradigm of treatment efficacy for skin and associated diseases.

In a global consensus on treatment transitioning, some situations have been named in which cessation of biological therapy can be justified with a careful follow-up (34). These include clearance of lesions for a minimum of a year, patients with a history of disease-free intervals or previously stable plaque psoriasis, absence of significant comorbidity or psoriatic arthritis and no disease worsening after previous dose reductions and treatment withdrawals.

Non-drug interventions

Interestingly, there is evidence for non-drug interventions as an effective measure for managing psoriasis. Investigations have assessed the effect of weight loss on psoriasis and conclusively found that the severity of psoriasis can be significantly improved. The most convincing data are derived from bariatric surgery where the majority of patients show a significant improvement of psoriasis severity (54,55). However, there are no data yet available that demonstrates a lasting effect of weight-loss measures on psoriasis severity/activity after the intervention.

In addition, several studies have shown that obesity impairs treatment response even when drugs were dosed according to body weight such as in the case of ciclosporine and with some biological therapy (56,57). Therefore, the integration of weight-loss programmes into psoriasis management procedures is mandatory.

Tobacco smoking was also demonstrated as an independent risk factor for psoriasis, but there is less evidence that smoking cessation leads to improvement of plaque psoriasis, whereas there are data on a beneficial effect in palmoplantar pustulosis (58,59).

Networking

Qualified care of patients with psoriasis requires appropriate networking that is adjusted to the setting-specific environment.

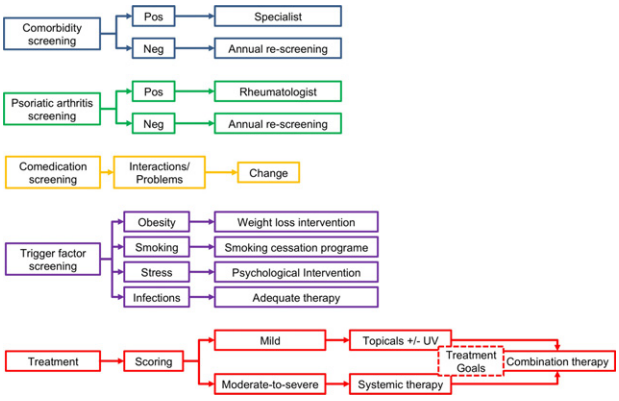

Figure 2. Concept of psoriasis management.

To adequately control comorbidity including psoriatic arthritis networking with other specialists is needed. Screening tools such as TOPAS or PEST for psoriatic arthritis and others such as the Beck depression scale may help to prescreen those patients who need to be seen by rheumatologists and psychiatrist/psychologist (60). In Germany, a screening algorithm for assessment of psoriasis comorbidity in general has been developed and published on an expert consensus basis (61). When treating associated diseases, the respective standards including treatment goals should be applied by the respective specialist.

Conclusion

The most important notion of the past years is to regard psoriasis as a systemic disease. For effective control of skin manifestation and associated conditions, appropriate management is required (Fig. 2). Establishment of quality controls including scoring of severity and integration of treatment goals enables efficacious drug therapy.

Management further includes screening for comorbidity and respective treatment or referral to specialists in a networking environment. Trigger factors should be identified and eliminated if possible. Associated conditions such as obesity and smoking need to be identified, and patients encouraged entering weight-loss and smoking cessation programmes.

As such complex management may not be feasible in a common dermatology practice, networking with psoriasis specialized centres at least for patients with moderate-to-severe psoriasis is a meaningful approach.

Author contributions

UM drafted the paper. KS and SG critically revised the manuscript and assisted with literature searches. UM, KS, and SG approved the final version of the manuscript.

Conflict of interest

UM has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, BASF, Biogen Idec, Celgene, Centocor, Eli Lilly, Forward Pharma, Galderma, Janssen, Leo Pharma, Medac, MSD, Miltenyi Biotech, Novartis, Pfizer, Teva, VBL therapeutics, Xenoport. KS has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of following companies: Abbott/AbbVie, Almirall-Hermal, Biogen Idec, Eli Lilly, Amgen, Janssen-Cilag, MSD, Novartis, TEVA, VBL therapeutics. SG has been an advisor and/or received speakers honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Celgene, Eli Lilly, Forward Pharma, Galderma, Janssen-Cilag, Leo Pharma, Medac, Merck Serono, MSD, Novartis, Pfizer, Sandoz Biopharmaceuticals, Schering-Plough, Teva, UCB Pharma, VBL therapeutics, Wyeth Pharma.

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Supporting Information

Additional supporting data may be found in the supplementary information of this article:

Figure S1. Proposed algorithm how to select currently available biological agents for plaque psoriasis with or without psoriatic arthritis or in severe, highly active plaque psoriasis. It is important to state that patient-related individual factors are essential for drug selection.