Inflammatory diseases – a new way of thinking

Author(s)
Jörg C. Prinz (joerg.prinz@med.uni-muenchen.de)

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Abstract
Psoriasis, psoriatic arthritis, ankylosing spondylitis and the inflammatory bowel diseases form a group of pathogenetically related and possibly co-occurring diseases. After its onset, psoriasis is usually a chronic disease that often requires lifelong treatment. Today, several groups of drugs are available for the treatment of psoriasis, with different characteristics, efficacy and safety. To use these drugs appropriately, we need to develop rational criteria and strategies. Decision making in psoriasis treatment should be tailored to the individual condition and needs of the patient, considering the life phase, associated diseases and co-morbidities. In addition to the acute improvement of the disease, psoriasis therapy should generate long-term perspectives that must be developed between the patient and the treating dermatologist and implemented in management concepts.
INTRODUCTION

The treatment of psoriasis has made tremendous progress over the last two decades and has become seemingly simple. A number of therapeutic biologics have been developed that causally intervene by blocking certain cytokines in the immunological cascade of the T-cell mediated autoimmune response of psoriasis. Thus, depending on the drug, an injection given at intervals of 2 to 12 weeks can significantly improve the course of psoriasis and psoriatic arthritis and in a substantial percentage of patients even completely clear the psoriatic symptoms. Recent drug developments include JAK/STAT and Tyk2 inhibitors of the Janus kinase pathway, small molecules that inhibit intracellular cytokine signalling. The mechanism of action of the drugs corresponds to several genetic associations of psoriasis, which, with common gene variants such as of TNFAIP3 (TNF alpha induced protein 3), TNIP1 (TNFAIP3 interacting protein 1), TRAF3IP2 (TRAF3 interacting protein 2), IL23R (IL-23 receptor), IL12B (p40 chain of IL-12 and IL-23), IL23A (p19 subunit of IL-23), TYK2 and STAT2, define central sites in the pathogenetic cascade of psoriasis. Several of these gene variants are pleiotropic and shared between different immune-mediated diseases, which are associated with each other as a complex of psoriasis, peripheral arthritis, ankylosing spondylitis and inflammatory bowel disease. They point to specific disease pathways and possible therapeutic approaches, which are reflected in the common response of psoriasis, peripheral arthritis, ankylosing spondylitis and IBD to, for example, IL-23 or TNF-α blockade [1]. The presentation made at 6th WPPACongress focused on individual aspects that may play a role in the decision for the respective drug from my own clinical experience. This presentation was not intended to constitute a review of psoriasis therapy as a whole. The congress took place in 2021. The content therefore reflects the state of affairs in 2021. At that time, no JAK/STAT inhibitors were approved for plaque psoriasis. Currently, there are comprehensive reviews available to fully address the current state of the art.

RATIONAL USE OF PSORIASIS DRUGS

Overall, this conveys the view: give an injection and the skin is clear. However, rational use of the appropriate medications should take into account that psoriasis is a lifelong disease after its onset, which usually occurs in adolescence or early adulthood. As a chronic inflammatory disease, psoriasis requires potentially life-long treatment. Consequently, psoriasis establishes long-term relationship between the patient and the treating dermatologist. The treating physician must adapt the treatment decisions to the current and future phases of life and to various and often unforeseen events. These aspects are not covered by clinical trials that select patients according to strict criteria that may not reflect life reality. They document the well-controlled exposure to treatment in rigorously selected patient populations that usually exclude real life aspects such as certain concomitant diseases, risk of associated disease, pregnancies and breast feeding, chronic or latent infections, history of malignancies and other life events. Therefore, common therapy concepts are much based on the question how fast and to what extent an improvement can be achieved. This may not always correspond to the actual patient situation and miss relevant necessities. Treatment concepts must take into account very different aspects such as the different prognoses of the diseases of the psoriasis complex. While in psoriasis a complete full reconstitution into a normal skin condition is clinically possible, arthritis and ankylosing spondylitis with the damage to the joints as well as inflammatory bowel disease (IBD) with scarring, stenoses, perforations and fistulas produce permanent impairment. The presence of arthritis and IBD with psoriasis therefore justify a more rapid access with early intensive intervention, while psoriasis of the skin allows for a slower and more restrained approach. For all these special
circumstances, experience-based therapeutic decisions must be developed together with the patient. Psoriasis management today means: Develop concepts, respond to circumstances and deliver solutions in accordance with the age, life circumstances and possible concomitant diseases of the respective patients. In addition to the direct improvement of symptoms, psoriasis treatment should create long-term perspectives. The lifelong need for treatment and exposure to medications should furthermore consider the principles of medical practice that were established by the physician Scribonius Largus at the court of Emperor Tiberius Claudius and have been valid since antiquity: Primum non nocere, secundum cavere, tertium sanare: First don't harm, second be careful and third cure the disease.

DEVELOPMENT OF LIFE PHASE-ADAPTED THERAPY AND MANAGEMENT CONCEPTS THAT CONSIDER FUTURE ASPECTS

Psoriasis treatment concepts must consider many aspects. Treatment should be tailored to the patient’s age, career developments, need for vaccinations, diseases associated with the psoriasis complex, concomitant diseases, and other aspects. In the family planning phase, drugs should be chosen that do not pose a later risk of malformation or teratogenicity. Overall, this requires early development of long-term treatment concepts that take into account the patient’s needs and the particular characteristics of the available drugs. National regulatory requirements may affect the treatment decisions. In different health care systems, such as in Germany, the less expensive, low-cost forms of treatment, such as phototherapy, fumaric acid esters, methotrexate, acitretin and ciclosporin, must be used first. Only when these drugs were not effective, could not be given because of contraindications or had to be discontinued because of side effects, the therapy may be escalated and biologics may be used. Then it is necessary to decide which cytokine should be blocked.

CHOOSING THE RIGHT DRUG

Biologics

Multiple aspects affect the choice of a particular biologic for psoriasis treatment [2, 3]. With the exception of infliximab, blockade of TNF-α is associated with a comparatively lower efficacy in psoriasis than the blockade of other cytokines, but generally has a higher risk of severe infections and exacerbations of latent tuberculosis. Especially in regions with a high tuberculosis prevalence, this may be problematic. A family history of multiple sclerosis is a contraindication. Nevertheless, TNF-α antagonists also have considerable advantages. With the exception of congestive heart failure, TNF-α antagonists are cardio-protective, reducing the incidence of cardiovascular events. They show well-established efficacy in concomitant psoriatic arthritis, ankylosing spondylitis and Crohn’s disease, which particularly justify their use when these diseases occur together with psoriasis. Furthermore, there are two representatives of the TNF-α antagonists that differ in structure from the cytokine antibodies. In etanercept, the extracellular domain of the TNF-α receptor is fused with an IgG-Fc part. This causes a short serum half-life and high application frequency of approximately three days, which, in comparison to the antibodies, allows a short-term discontinuation of therapy in the case of infections and is thus easily controllable. Furthermore, etanercept is not contraindicated in patients with hepatitis C virus infection and can even reduce the viral load. In certolizumab pegol, a humanized antigen-binding fragment (Fab’) of a TNF-α antibody has been conjugated to a polyethylene glycol residue. The absence of the Fc region prevents transplacental transfer or transfer into breast milk, thereby avoiding drug exposure of the fetus or newborn. Accordingly, certolizumab is the most preferred agent for the treatment of pregnant or lactating women and should be kept in reserve for this indication in female patients of childbearing
The IL-17 antagonist bimekizumab shows the highest efficacy and the fastest onset of therapeutic efficacy in psoriasis [4-7]. The IL-17 antibodies are also approved for psoriatic arthritis and ankylosing spondylitis. However, the high efficacy is accompanied by an increased risk of candida infections. Especially in patients with concomitant diabetes mellitus, who per se have an increased risk of candidiasis, or in patients with a history of urogenital candidiasis, IL-17 antibodies should be used cautiously. Furthermore, IL-17 blockade can trigger inflammatory bowel disease. Before prescribing IL-17 antibodies, the presence of IBD in the patient and in the family history should be excluded. Blockade of interleukin (IL-) 23 or of IL-12/IL23 allows long application intervals. Compared to the somewhat faster-acting IL-17 antibodies [8], they have a better safety profile lacking Candida infections [9]. They are also effective in peripheral psoriatic arthritis and especially in enthesitis and dactylitis, but are not sufficiently effective in ankylosing spondylitis. Instead, they show superior efficacy in IBD accompanying psoriasis. The efficacy of fixed-dose biologics decreases with increasing body weight. The weight-based dosing of infliximab and ustekinumab makes the two biologics particularly suitable for the treatment of obese patients. The risk of developing anti-drug antibodies when biologic therapy is interrupted is highest for TNF-α antibodies and secukinumab. Therefore, a biologic treatment should always be conducted as a continuous therapy, since an interruption of the application can cause a loss of efficacy and thus of the drug for the patient [10, 11].

Conventional anti-psoriatics

Despite the high efficacy and documented safety of biologics, conventional anti-psoriatics still have a role of their own [12]. Non-biological drugs have the advantage that their effectiveness can be better controlled by a rapid termination in the event of adverse events or other unforeseen occasions such as the need for vaccination, infections or trauma. Unlike biologics, they do not induce the formation of anti-drug antibodies that would prevent a response to retreatment. Methotrexate has cardioprotective effects. It is therefore particularly suitable for elderly patients with a high cardiovascular risk. Ciclosporin can produce rapid remissions of psoriasis as an acute intervention for short treatment periods of several months without much risk of adverse events, as may be required presurgically or for other life events. It may induce remission in patients with refractory Crohn's disease, and it may be used in pregnant women. However, nephrotoxicity limits the duration of ciclosporin use to a few months, so it doesn't offer a longer-term perspective. Acitretin is particularly suited in patients with a history of malignancy, although the expected efficacy is much lower than with other drugs. Fumaric acid esters are a first-line therapy when available (approved in the European Union). If tolerated and effective, they can control psoriasis with a long-term perspective. However, their use should be discontinued if lymphopenia occurs, which can be prolonged and is then a contraindication to other medications, such as methotrexate or ciclosporin. The use of conventional anti-psoriatics is in turn limited in the presence of other diseases of the psoriasis complex. In psoriatic arthritis, only methotrexate offers a certain perspective, as it improves inflammation but not radiographic progression of joint damage. This makes it a basic treatment in psoriatic arthritis that usually has to be supplemented by suitable biologics. Inflammatory bowel disease is not adequately controlled by any of the conventional drugs in the long term; in this case, the immediate use of TNF-α antagonists or IL-12/IL-23 or IL-23 antibodies is justified.

Novel small molecules

The phosphodiesterase-4 inhibitor apremilast is active in psoriasis and psoriatic arthritis, although the expected effectiveness is quite low. Due to the lack of drug-drug interactions, apremilast is particularly suited for the treatment of patients with multiple concomitant medications. As with acitretin, a history of malignancy is not a contraindication, while depression limits the use of both drugs. For the inhibitors of the JAK/STAT
cascade [13] and of Tyk2 [14], there is still too little experience from the long-term exposure of psoriasis patients yet. They are at least a reserve strategy for psoriasis and psoriatic arthritis when other drugs have failed. Effects beyond immunomodulation generally implicate a lower specificity for the pathogenic immunological cascade of psoriasis and thus entail a new spectrum of adverse events, including the (rare) occurrence of thrombosis and thromboembolism.

**Childhood psoriasis**

Most biologics are now approved for childhood psoriasis from a certain age on. Here, efficacy and safety correspond to the use in adults [2, 3]. The conventional anti-psoriatic drugs methotrexate, ciclosporin and acitretin are considered safe and effective for short-term administration. While premature closure of epiphysis by acitretin cannot be ruled out, no effects on the skeleton have been observed and the administration of acitretin in this age group is considered largely safe [15].

**DECISION MAKING – A PERMANENT CHALLENGE IN PSORIASIS TREATMENT**

The different properties of psoriasis medications imply different decision criteria. This includes trying to adapt drugs to patient age and, if possible, avoiding drugs that may have a unique benefit in later stages of life. In women of childbearing age, keep certolizumab in reserve for later pregnancy. Consider methotrexate in elderly patients with cardiovascular diseases. Consider medicines with a short half-life and the possibility of flexible dosing in infectious conditions or when surgery is required. Consider weight-based medications for overweight patients. Avoid IL-17 blockade and acitretin in patients with a family history of inflammatory bowel disease. Avoid TNF blockers in patients with a family history of multiple sclerosis. Avoid acitretin or apremilast in patients suffering from depression. Use ciclosporin for short-term remission if rapid clearance is required. Don’t interrupt biologic therapy unless required to avoid formation of anti-drug antibodies. Use phototherapy, acitretin or potentially apremilast in patients with a history of malignancy.

**INFLAMMATORY DISEASE – A NEW WAY OF THINKING: SOME CONCLUSIONS FROM 30 YEARS OF PSORIASIS MANAGEMENT.**

Psoriasis belongs to a group of pathogenetically related diseases and has comorbidities, all of which must be considered in the treatment decision. Today, there are numerous treatment modalities available with different characteristics. Efficacy must not be the sole criterion for a particular drug or treatment. To use these drugs appropriately, we need to develop better criteria and strategies that are adapted to the actual patient condition, take into account the current and later phases of life, consider family history and other aspects. Accordingly, decision-making in psoriasis treatment should be tailored Case by Case and Phase by Phase (of life).

**AUTHORS’ CONTRIBUTIONS**

J.C.P. wrote the manuscript.

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