Psoriasis: implications of biologics
Lecluse, L.L.A.

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General discussion
GENERAL DISCUSSION

Without any doubt, the biologics form a welcome addition to the treatment armamentarium for patients with moderate to severe psoriasis. Before the introduction of the biologics, a considerable amount of these patients was repeatedly hospitalized for exacerbations or uncontrollable disease. For many of them, treatment with a biologic has been life-changing and is even called ‘miraculous’ by some patients.

However, at this moment it is not desirable to bypass the conventional systemic therapies for moderate to severe psoriasis and turn to the biologics straight away. Firstly, because of the high burden it would put on the health care budget. Secondly, since long term risks of the biologics are not known yet. As said in the introduction, malignancies associated with PUVA appeared to develop 15 years after exposure to this therapy. There are currently no long-term data on treatment with biologics for psoriasis available. We can learn from experiences in rheumatology and gastro-enterology, but the patient populations differ. Psoriasis patients have in most cases been exposed to photo(chemo)therapy in the past which increases the risk of cutaneous malignancies. Further, the populations suffer from different comorbidities and use different concomitant therapies. Until long-term safety data are available, patients to which biologics are prescribed should be carefully selected.

This is illustrated by the fact that marketing authorization for efalizumab was suspended less than five years after its introduction as a result of rare severe adverse events. Three patients developed progressive multifocal leukoencephalopathy (PML) after using efalizumab for more than three years. The EMEA then considered the benefits to no longer outweigh the risks of efalizumab.

For all individual patients using a biologic, benefits and risks should be weighed at every visit. No general comments can be given since these considerations are multi-factorial. Items for consideration are severity of the disease, treatment effectiveness, patient satisfaction, medical history, comorbid disease, concomitant medications, alternative treatment options, antibody development and occurrence of adverse events.

For most patients who are treated with biologics for psoriasis, treatment alternatives are scarce. Therefore, managing factors that impair treatment is important. One of these factors is the occurrence of adverse events, which may lead to cessation of treatment. This thesis offers a helping hand for the management of infliximab related infusion reactions and etanercept related dermatological adverse events.
Another factor that may impair treatment is loss or lack of response. For adalimumab we showed that antibody formation plays a considerable role in non-response. For other biologics, it is still under investigation to what extent antibodies are formed and what their clinical consequences are for psoriasis patients. Neutralizing antibodies have never been found in patients treated with etanercept as opposed to patients treated with infliximab. Anti-infliximab antibodies have even been associated with an increased risk of infusion reactions in patients treated for other indications (see chapter 3).

The knowledge that formation of antibodies to the biologics may result in loss of response, leads to new questions. What are risk factors for antibody formation? Long interruption of treatment seems to be one and maybe previous treatment with other biologics. Genetic predispositions should also be considered and need further investigation. How antibody formation can be influenced is another question. As discussed in chapter 6, a positive role for concomitant methotrexate is suggested. For psoriasis patients this needs to be confirmed and if so, an optimal dose should be found.

Although still many issues need to be sorted out considering the available biologics, new biologics are already in the pipeline and one has even recently been registered (ustekinumab). This is yet another reason for establishing large registries that collect long-term data.

**Future considerations**

Hopefully one day, the possibility will be there to predict beforehand to what therapy patients will respond satisfactorily. This would save patients periods of ineffective treatments and the occurrence of adverse events. Furthermore, it would save society unnecessary high healthcare costs. Identifying different genotypes in psoriasis patients using large DNA-databases might be the key. Furthermore, since several genes are known to play a role in the pathogenesis of psoriasis, maybe some day psoriasis may actually be cured by means of gene therapy.

Until then, we need to accept that patients with psoriasis probably need lifelong therapy and therefore treatment with these therapies should be as effective and safe as possible.