Innovative therapies and new targets in psoriasis

de Groot, M.

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GENERAL DISCUSSION
CURRENT BIOLOGICS

Without a doubt, the arrival of biologics has meant a big step forward for the treatment of psoriasis patients with moderate to severe psoriasis. Randomized clinical trials as well as prospective\textsuperscript{1,2} and retrospective cohort studies on biological treatment in daily practice, like the study presented in Chapter 3 with etanercept\textsuperscript{3}, clearly show great clinical improvement of psoriasis in patients treated with biologics. Furthermore, a large proportion of patients treated with biologics indicate a substantial improvement on health-related quality of life\textsuperscript{4}.

However, although the clinical improvement by some these of immunosuppressive biologics is impressive, the situation is still not optimal. There are still some serious side-effects, like drug eruptions as presented in Chapter 2, and long-term safety of biological is a concern. Biologics are associated with increased infections (tuberculosis, aspergillosis, etc), malignancies (lymphoma), haematological disorders and demyelating disorders (multiple sclerosis)\textsuperscript{5,6}. The formation of autoantibodies and antibodies against biologic drugs themselves can occur causing impaired treatment outcome or even giving rise to certain side effects\textsuperscript{7-10}. Also, with regards to the TNF\textsubscript{α} antagonists, there is a growing number of reports mentioning the paradoxical onset or worsening of psoriatic skin lesions during treatment with TNF inhibitors\textsuperscript{11,12}. Besides side-effects and long term safety, the high costs are another factor limiting the widespread use of biologics. The average medication costs for a treatment with a biologic per year are € 12 000\textsuperscript{13} and in case of non-optimal response requiring a double dosage, costs rise accordingly. In the future however, generic biologics will become available, making the costs less excessive.

As to clinical improvement, it is questionable whether new therapeuticals will be able to exceed the current clinical advances with regard to improvement of PASI. Ustekinumab and infliximab are already able to reduce PASI with 80% and the difference between 80% and 95% PASI improvement is almost negligible.

In clinical practice these new biological drugs have been remarkably well tolerated, but we have relative short-term safety data, for some biologics (like ustekinumab) even shorter than others (like etanercept), and need to continue to monitor these patients for long-term safety. National registries are of the utmost importance for collecting these data. Information from these registries will help us to guide strategies for long-term disease management of psoriasis.

FUTURE DIRECTIONS

Despite numerous recent advances in the treatment of psoriasis, it remains still a very recalcitrant disease to treat. For example, we cannot predict who is likely to respond well to a particular therapy and who will not. There are two major areas where we can expect to see further developments that may profoundly affect our ability to
help psoriasis patients in the future. First, continued advances in the understanding of the complex immunologic pathways that contribute to the chronic inflammatory state in psoriasis will certainly lead to the discovery of new targets and development of additional interventions. Second, personalization of treatment based on genetic and demographic characteristics may lead to better and safer outcomes in patients.

With regards to continued advances in the understanding of the complex immunological pathways that contribute to psoriasis lesions, the discovery that certain chemokines and their ligands that are upregulated in psoriasis (Chapter 6 and 7) may be a potential therapeutical target. Currently, several chemokine inhibitors are approved by the FDA for the treatment of several diseases. In 2007 maraviroc, a CCR5 inhibitor, was approved for prevention of HIV and in 2008 a CXCR4 antagonist was approved for hematopoietic stem cell mobilization. Furthermore, recent result of a phase III trial with a CCR9 inhibitor for Crohn’s disease are promising. Novel chemokine antagonist-based strategies to interfere with skin inflammation are rather preventive than therapeutic. Chemokine antagonist could be excellent tools to impair the recruitment of pathogenic leukocyte subsets to the skin. Once leukocytes have entered the skin and underwent activation processes, chemokine antagonist are supposed to be less effective. In combination with established drugs, such as methotrexate, cyclosporine, phototherapy or biologicals, however, chemokine antagonist could be promising candidates for prevention of acute flares, prolongation of lesion-free interval and therefore provide optimized long-term management of this chronically relapsing disease. Chemokine antagonist could be an effective additional treatment in patients with specific phenotypes of psoriasis, like pustular psoriasis, where accumulation of neutrophils causes the specific phenotypic features.

Evolving insight in the pathogenesis of psoriasis has led and will lead to the development of new treatment options. In order to prove its clinical efficacy and safety, large numbers of patients have to be tested. Yet, large randomized controlled trials will become more difficult to perform: fewer psoriasis patients match up to the proposed inclusion criteria, whereas the number of candidate therapeuticals is ever-growing. Moreover, due to availability of effective treatment for a large number of psoriasis patients, their willingness to participate in clinical trials diminishes. In psoriasis only limited data on biomarkers are available. Therefore, research regarding identification of biomarkers (Chapter 4-5) that could be used for prediction of the clinical response to treatment is necessary, enabling quick assessment of the efficacy of new treatment modalities in a small number of patients.

With regards to personalized treatment, pharmacogenomics may play a role in the future for psoriasis patients. Gene expression profiles could predict response to therapy or risk for side effects, preventing unnecessary periods of ineffective treatments (and thereby frustrations in patients and physicians) and consequently unnecessary high health care costs. Also, new targets could be identified that may lead to specific treatments. Several psoriasis-associated heritable loci have been identified, and the increased expression of several genes has been identified, but a
marker that predicts therapeutic response has yet to be identified. And perhaps, with the increasing knowledge of responsible genes in psoriasis, one day psoriasis may actually be cured by means of gene therapy.

Until then, we need to continue the research and keep the therapeutic pipeline active and productive.

REFERENCE LIST