Old, new and emerging systemic therapies for atopic dermatitis

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Atopic dermatitis (atopic eczema) is the most common skin disease. Although the disease is not life-threatening, it has a deep impact on the patients' life quality and their relatives. About 15-20% of the new-borns will be affected by this condition. For unknown reasons, the disease will go into remission before puberty in about 50% of the cases and may eventually relapse a few years later but also in many cases up to thirty or fourty years later. Thus, the disease course is unpredictable and confronts the physician constantly with new challenges regarding the optimum management.

The classic therapeutic approach

The current management of the disease is based on three main pillars: (i) Improving the disturbed epidermal barrier by the use of emolliens on the one hand and (ii) controlling the chronic inflammatory response on the other hand. Beside this, (iii) an allergological work-up should be done based on the age of the patient (30% of the children may have a food allergies driving the flares) and individual history which is almost unpredictable.

The use of emolliens to improve the epidermal barrier function is now recognized as the basic therapy for atopic dermatitis. The use topical steroids as first line therapy is still the "golden standard" in the management of this disease for most mild and moderate forms. The introduction of the topical calcineurin inhibitors (TCIs) almost twenty years ago has substantially improved the armamentarium for the treatment of mild, moderate and even some severe cases of atopic dermatitis. One of the most important progresses within the last decade was the introduction of the so-called proactive management. This led to a fundamental change of mind of the patients and their physicians, trying not to concentrate on the treatment of flares, but rather to find some new ways to control the disease on the long term by the topical application of anti-inflammatory compounds in addition to the regular basic therapy.

For the more severe cases, up until recently, only ciclosporin A (CSA) was officially approved for the treatment of these patients. However, the clinical experience has shown that CSA cannot be considered as monotherapy and is very often limited by its nephrotoxicity, particularly in older patients. The use other immunosuppressive compounds such as methotrexate, as therapy or mycophenolate mofetil is by definition an off-label prescription and shows substantial variation in terms of responsiveness among the population of patients treated so far. Therefore, there is still a real need in the management of patients suffering from severe atopic dermatitis due to the very limited spectrum of approved compounds.

Biologics and small molecules

Besides the above-mentioned immunosuppressive compounds, a new class of drugs is now entering the scene for the treatment of moderate to severe atopic dermatitis. Indeed, recently, the first biological targeting the key cytokines, IL-4 and IL-13, has been approved in the USs and in Europe. The results of the phase II and the phase III studies leading to the approval of Dupilumab should fulfill the expectations of a substantial proportion of the patients suffering from moderate to severe atopic dermatitis. Besides Dupilumab, a number of other biologics are currently in the pipeline of the pharmaceutical industry, such as Tralokinumab and Lebrikizumab both targeting IL-13. Other strategies targeting either IL-31 (Nemolizumab) or IL-5 (Mepolizumab) but also TSLP (Tepezelumab) are currently in clinical development programms. Besides the biologics, a number of small molecules are also currently in development and are interfering with the JAK-Kinase family with more or less specificity. Another popular target since the 1980s remains blocking PDE4 by topical means such as Crisaborole (approved in the US for mild to moderate cases) or Lotamilast which is still in development. Finally, a new molecule directed against the histamine receptor type 4 (H4R) has recently shown to have some effects in this condition in a proof of concept study.

Management of atopic dermatitis

The complexity of the disease, the lack of predictability of the emergence of allergies potentially leading to the so-called "atopic march", the influence of the chronic skin inflammation on the brain (the so-called "atopic psychiatric march") have all questioned the common unified concept of the disease and its pathophysiology. The discovery of several genes involved in the dysfunction of the epidermal barrier and the different immunological mechanisms leading to the chronic inflammation and the emergence of allergies explain partly the high complexity of clinical phenotype of this condition. More insights into epigenetic regulation of the barrier function

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and the immunological mechanisms will add another level of complexity. Therefore, it is obvious that - similarly to what we have seen in the last decade in oncology - a new strategy should be designed, away from the "one-size-fits-all"-concept. The trend is towards personalized diagnostics as well as preventive and therapeutic approaches. This so-called precision medicine-approach can only be achieved with the help of sophisticated and innovative research projects dealing with a better understanding of the natural history of the disease and the underlying mechanisms as the driving forces of this complex phenotype. Thereby, comprehensive registries and biobanks will be instrumental for the discovery of diagnostic, predictive and prognostic biomarkers for atopic dermatitis. Also, registries including patients who have been put under new therapies such as biologics and new small molecules will be extremely helpful in order to stratify the complex phenotype in terms of responsiveness to new drug developments. Moreover, in terms of prevention, predictive and prognostic biomarkers will enable us to get reliable information with regards to the fate of the disease and the risk to develop an "atopic march" in a very early state of the disease. Ultimately, the goal should be to develop new disease modifying strategies which will hamper the occurrence of AD selectively in new borns at high risk. Such strategies will also block the emergence of allergic sensitization and the evolution of the atopic march.

Conclusion

We are currently experiencing tremendous progress in our understanding of the genetics and immunological background of atopic dermatitis. At the same time, we realize the complexity of the clinical phenotype and should focus our efforts and research investments to new approaches aimed to stratify the complex and heterogeneous phenotype into more homogenous subgroups for which either the conventional approach or a more sophisticated therapeutic management will be needed to reach the goal of a truly individual management.

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