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New opportunities and challenges in the assessment of drugs for atopic diseases

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Abstract

Atopic conditions (atopic dermatitis, rhinitis and asthma) belong to the most common non communicable diseases and are driven by chronic inflammatory reactions. They have a strong impact on the quality of life and represent a substantial and growing socio-economic burden. Interestingly, there is an increasing interest in the development of new therapeutic options with a number of biologics and small molecules targeting potential key mechanisms in atopic conditions. However, besides the safety issue, most of the new active substances are still evaluated according to the traditional efficacy paradigm focusing on the success in treating exacerbations and flares. Instead, the future approaches in drug development and assessment should rather concentrate on the long term control of these diseases and consider their potential as disease modifying strategies in the era of precision medicine. To reach this goal, a number of unsolved issues have to be addressed and consensually accepted by the stakeholders in this field. Thus, a successful and rapid development of new treatments requests a paradigm shift and a new way of thinking in the mind of physicians, pharmaceutical industry, regulators and HTAs. This seems mandatory in order to optimize drug development and to facilitate the accessibility of new therapies to the growing population of patients suffering from atopic conditions on a global level.

Conflict of interest:

The authors state that they do not have conflict of interest relevant for this publication.

1. Introduction

Allergic diseases belong to the most frequently encountered diseases for which epidemiological studies have shown a worldwide increase in prevalence (1). Among allergic diseases, the so called atopic conditions, i.e. atopic dermatitis (AD), allergic rhinitis (AR) and allergic asthma (AA) represent the most frequent conditions and represent a substantial social-economic burden (2). This holds true not only in developed countries but also in an increasing manner in many of the other countries where the improvement of hygiene conditions has been assumed to be at least partly responsible for the emergence and development of allergic diseases. The allergen specific immunotherapy (AIT) represents probably one of the oldest therapeutic interventions (first reported in 1911), aimed to address atopic diseases at their initial roots, that is the sensitization phenomenon and the production of allergen specific IgE (3, 4). However, even if it is well accepted that this approach is effective in some subgroups of patients suffering from AR (2) and AA (5), and potentially in AD (6), after more than 100 years, we still do not fully understand the precise mechanism of action (4, 7). In contrast, intense research in understanding the basic mechanisms of IgE-mediated sensitization and atopic diseases has unraveled an impressive number of assumed key-players involved not only in the phenomenon of sensitization but also in the effector mechanisms leading to clinically relevant symptoms.

2. Impact of research progress on new diagnostic and therapeutic developments

While in the 80's and 90's, atopic conditions were considered to be the product of an immunological Type 2 (Th2) dominance, the current view of the pathophysiology of these conditions has dramatically changed (8-10). More recent findings have strongly supported the notion that each phenotype in fact recognizes several different endophenotypes which are themselves driven by distinct key-cytokines and other mediators not necessarily linked to T2 type of immune response. This progress has led to a number of reports aimed to refine the clinical phenotypes of AD, AR and AA according to a complex constellation of various candidate biomarkers (9, 11, 12). Although most of these biomarkers have not yet been validated and their fitness for use remains to be demonstrated, they potentially represent interesting tools for the

improvement of the differential diagnosis of atopic conditions and for their future stratification. On the other hand, some of them may also represent interesting candidate targets for new therapeutic approaches using either small molecules or biologics. Therefore, it is expected that in the near future, the gold standard in the management of atopic conditions mainly based on the use of local steroids either as inhalation, nasal solutions or topical creams and ointment, will be reconsidered since a new generation of active substances aimed to address the above mentioned key-players in atopic conditions will likely receive their marketing authorization (13, 14).

3. Paradigm shift in the therapeutic approach and management of allergic diseases.

The current approach: Treating the flares and exacerbations.

Besides ASIT which represents the only causative treatment, most other approaches have focused on the treatment of flares and exacerbations of the individual diseases. Therefore, most of the approved drugs in the field of atopic conditions have been primarily tested and approved on the basis of the ability to treat a flare and exacerbation in clinical trials typically lasting for a rather limited period of time, e.g. up to 16 to 32 weeks. This is particularly true when considering the trial designs used in the context of proof-of-concept studies which would first show the efficacy of a given compound in reducing the immediate severity of patients typically affected by moderate to severe forms of a given condition. With this regard, it is not surprising, that steroids remain the most valid and rapid acting compounds able to reduce the severity of either AD, AR or AA as witnessed by the medical guidelines (15-17). In AD, topical calcineurin inhibitors may be used as second line therapy (18). Thus, the current and classical study design focusing on the treatment of flares and exacerbations may well help to appreciate the efficacy of a given approach for the peak situations in the chronic inflammation, but does not answer the question whether this particular treatment is able to control the disease on a long term. Indeed, it is not excluded that some new compounds fail to be able to treat the flares and exacerbations while their actual potential more resides in the long-term control of the disease.

The new approach: Controlling the disease on the long term.

With the available treatment options using steroids, treating a flare or exacerbation is not a difficult task, to control the disease is the real challenge. For example, this can be reached in the management of AD with the long term of topical tacrolimus (19) and can potentially save medical costs (20). However, long term control could potentially be reached with the help of biologics aimed to target key-mediators, their receptors or cells involved in the chronic inflammatory processes in allergic and atopic conditions. It is anticipated that most of these compounds have a rather slow or delayed action and it cannot always be expected that they can be efficiently used for treating acute flare or exacerbations. Therefore, a paradigm shift must be introduced which will affect the current and future strategies in drug development and particularly in the design of clinical trials in order to emphasise on the long term control in the management of atopic conditions. However, in order to successfully implement this strategy, a number of unsolved issues need be addressed (see below).

The future approaches: Stratification of patient populations and disease-modifying strategies in atopic conditions.

Assuming that the new generation of compounds will be potentially able to control the disease on the long term and potentially avoid comorbidities (21-23), the next questions which are obviously to be answered is to (i) whether all patients will respond in the same way and (ii) whether the future compounds have the potential to be used in some subpopulations of patients for very early intervention (i.e. in early childhood) in order to stop the atopic march. It is well accepted, that AD most probably represents the first step of the atopic march (24) and, providing the safety profile and the benefit-risk-ratio issues are solved, it is worth to invest efforts in trying to reach the goal of a disease modifying strategy (25). Due to the broad spectrum in the phenotype and natural history of the disease, it is expected that this kind of strategy most probably will be applicable for a sub-group of patients, e.g. those affected by a very early onset and suffering from a rather severe form of AD. However, the discovery and validation of appropriate biomarkers is urgently needed in order to best guide the therapeutic and preventative approaches in the context of

precision medicine. Finally, since the new generation of compounds aims to target key-cytokines involved in the chronic inflammatory process of atopic conditions, it cannot be excluded that some of these new approaches may even be able to reverse the atopic march in distinct subpopulations of atopic individuals.

4. The unsolved issues for the paradigm shift

In order to reach the above mentioned goals, a number of unsolved issues which have been partially addressed (26, 27), remain to be fixed and validated by the scientific community and find agreement from the other stakeholders such as regulatory agencies, pharmaceutical industry and payers or the health technology assessment agencies (HTA). The following – non comprehensive - list of unsolved issues of relevance in the context of clinical trial design may give an impression of some major aspects to be addressed in the near future (NB: not all issues are relevant for all atopic conditions). Some of these points have been partially addressed

- How to define the unmet need?
- How to define inadequate response to a given treatment?
- How to define a flare or exacerbation?
- How to define disease control?
- What is best supportive care (typical example where scientific communities have failed and HTA's established their own definition)?
- How to define and measure the clinical minimal important difference to placebo (CMID) for the various endpoints and PROs?
- How to measure itch in atopic dermatitis?
- How to measure the consumption of rescue medication or of accompanying treatment?
- How to define a risk-group for a given disease?
- How to define and measure disease modification?
- How to improve compliance in clinical trials and in real-life as well as other aspects of behavioral medicine?

These seemingly trivial questions have only partly been addressed and solved so far for some of the atopic conditions. They could be implemented in regulatory guidances once they have found consensus among the stakeholders. They would allow speeding up drug development programs as well as allow more comparability between different trials and medicinal products.

5. The issue with patients registries

Patient registries have recently been recognized as important tools to collect data related to the history of a disease typically in connection to exposition to one or several active compounds in the context of in-label or off-label use. Obviously, the interest for patients registries is driven by different kind of requirements depending on the stakeholder's purpose in collecting the data.

As an example, academia may be interested in scientific issues such as getting insight into epidemiological or pathophysiological aspects. They represent valuable instruments for clinical research planing or for updating guidelines. Also registries are of primary value in conjunction with a biobank approach, for the discovery of particular bio-markers with a diagnostic, prognostic or predictive value.

On the other hand, the industry is more interested in the data set for the assessment of safety aspects in the context of pharmacovigilance issues and risk-management-systems. This motivation is shared by the regulatory agencies which consider patient registries as important tools in monitoring the safety of established and newly marketed medicines.

Finally, the HTAs may be more interested in data related to real-life clinically use and aspects which are more in the field of their primary interest, i.e. comparative effectiveness or cost-effectiveness of already approved or newly marketed medicinal products.

We are currently observing a multiplication of patient registries in the field of atopic conditions but, as already noticed by the European Medicine Agency (EMA) in their recent initiative for patient registries, there is still a lack of common protocols, scientific methods and data structures as well as a lack of data sharing and transparency and finally, a lack of sustainability (28). The pharmaceutical industry is typically requested by the regulatory agencies to establish patient registries,

specifically for one given medicinal product, e.g. in the context of the new pharmacovigilance legislation in Europe. On the other hand, the academia should adhere to the forthcoming tactical specifications related to the core elements of standard protocol and common data elements as well as standard methodology and guidance on data privacy rules which should be applied to the registry data banks as requested by the regulators. These efforts should lead to an optimized landscape of patient registries with avoidance of duplications. The data could be shared by most stakeholders and fulfill their requirements in terms of quality for their own purposes.

6. Conclusion

As a consequence of the recent progress in our understanding of the pathophysiology of atopic conditions and the interrelationship between AD, AR and AA in terms of comorbidities, we currently see a dramatic and welcomed increase of potential new targets for promising medical products. These aim not only to treat the flares and exacerbations but bear the important potential to control a disease on the long term and ultimately to act as disease-modifying strategies. However, a successful and rapid development of new treatments requests a paradigm shift and a new way of thinking in the mind of physicians, pharmaceutical industry, regulators and HTAs. This should improve the complex processes of drug development always having in focus the safety profile but also looking ahead to serve the community of patients suffering from atopic conditions known to have a debilitating impact on their life.

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