Translational Research and Drug Development in Psoriasis by Collaborative Efforts of Academia and Industry

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INTRODUCTION

We are witnessing the wider implementation of new treatments for psoriasis, which are resulting from the research on genetics and pathogenesis and the development of new targeted treatments. Some developments during the past 20 years shall be highlighted and then projected in the perspective of new insights into the disease and new principles of care designated as precision medicine, stratified medicine, or personalized medicine, while reconciling the reality in daily practice that every patient has his own disease.

Innovative research and drug development—from fragmentation to consolidation

Several academic laboratories around the world have explored the pathogenesis of psoriasis and studied the different modes of action of treatments. The interaction between work in these laboratories and clinical units of academic departments has yielded new insights into the pathogenesis of different clinical phenotypes of psoriasis. The development of real-world evidence, using patient registries, has contributed to the insights into disease stratification by outcome (Augustin et al., 2016; Davison et al., 2017). Patient registries permit a systematic analysis of the course of the disease and the value of treatments over time (Carretero Hernández et al., 2018; Singh et al., 2018; van den Reek et al., 2018). Dermatologists are continuously working in a learning health care environment, collecting clinical practice real-world evidence, and investigating and integrating the potential predictive value of biomarkers in a real-world setting (Dand et al., 2019; Loft et al., 2018).

Research and development at pharmaceutical industries has resulted in a revolution of innovative treatments and new drug development methodologies over the last two decades. On one hand, the insights into the pathogenesis of psoriasis have guided drug development, and on the other hand, successful drug discovery has proven that tumor necrosis factor-α, IL-17-, and IL-23 signaling are actually relevant in pathogenesis and not just an epiphenomenon. The impressive efficacy/safety ratios of these targeted drugs were beyond imagination 20 years ago (Erichsen et al., 2019).

The collaborations between pharmaceutical industries and clinical research centers are condition sine qua non in the current drug development scenario. In the perspective of optimal positioning of innovative treatments, some reflections on this precious collaboration are warranted.

TRANSLATIONAL RESEARCH AND TREATMENT INNOVATION

Insights into pathomechanisms have identified new targets for drug development

In the past, the apparent efficacy of a treatment inspired us on the pathogenesis of psoriasis. Cyclosporine was effective in psoriasis and stimulated research on the immunology of the disease. The discovery that anti–tumor necrosis factor drugs are effective in psoriasis and psoriatic arthritis coincided with the research on tumor necrosis factor–driven processes in the pathogenesis and yielded a spectacular innovation in the treatment of psoriasis, which is evidenced by clinical trials and dramatic reductions in inpatient episodes in real-life practice (Fonia et al., 2010). Insights into the cellular immunology of psoriasis and involvement of dendritic cells coincided with the development of ustekinumab, which targeted IL-12 and IL-23. Through immunologic and genetic research, we learned that targeting IL-17 and IL-23 proved to be the way forward, further raising the bar from Psoriasis Area Severity Index (PASI) 75 to PASI 90 or even PASI 100 as the treatment goal.

Genetic research has also informed us that tyrosine kinase 2, encoding for a JANUS kinase, is a primary psoriasis susceptibility gene (Dand et al., 2017). This is a discovery that is paralleled now in drug development. BMS-986165 is a small molecule that inhibits tyrosine kinase 2. In phase 2 studies, this molecule has been shown to result in a PASI 75 in 80% of the patients (Papp et al., 2018).

The collaboration among clinical centers, research institutions, and pharma industries holds the promise of a new long-term perspective for patients with psoriasis.

Insights into pathomechanisms have opened new approaches in treatment monitoring

In oncology and hematology, the use of biomarkers has become the standard of care: predicting the course of the...
disease and optimizing the treatment selection and monitoring. In the treatment of psoriasis, we have not yet reached the stage of a broad implementation of codiagnostics in the management. For the treatment of psoriasis, biomarkers are needed to inform us on the likely course of the disease, including the development of comorbidities and to help us in the selection of the best treatment and how best to monitor the outcome.

Several studies have shown that blood levels of adalimumab may vary widely. In some patients, adequate drug levels are not reached, whereas in other patients, they are. A therapeutic range for blood levels of adalimumab has been established (Mahil et al., 2013; Menting et al., 2015). The evidence is available that measuring blood levels in clinical practice has value. Validation and health economic studies are required to assess the utility in real-life practice. However, clinical practice is awaiting implementation.

Genetic markers predicting the course of treatments are sparse. Single-nucleotide polymorphisms associated with anti–tumor necrosis factor responsiveness have been reported: rs11096957 on TLR10, JAG2, and ADRA2A (Nishikawa et al., 2016). More HLA-Cw6–positive patients on ustekinumab achieved a PASI 90, in particular after 6 months of treatment than the HLA-Cw6–negative patients (Dand et al., 2019). However, validation studies are required for the aforementioned pharmacologic studies.

Genetic studies have suggested that associated single-nucleotide polymorphisms may be predictive of the development of psoriatic arthritis (Patrick et al., 2018). Combining statistical and machine-learning techniques, the authors showed that the underlying genetic differences between psoriasis subtypes may carry a different risk in developing the subtypes of psoriasis (Patrick et al., 2018).

In a multifactorial polygenic disease such as psoriasis, it is feasible that computational models will be required for predicting the course of the disease.

**New perspectives in disease management**

With the implementation of new treatments for psoriasis, compelling questions for future research and development have to be answered. The dermatologist realizes that treatment selection has to be individualized. The question arises, to what extent the traditional disease classification “mild-moderate-severe psoriasis” is limiting access to biologic treatment? In several countries, it is a requirement for prescribing a biologic that the patient has at least moderate—severe disease, that is, PASI > 10 and body surface area >10, although patients with less extensive psoriasis may suffer from psoriasis severely. Recently, the International Psoriasis Council has published a new concept for the assessment of disease severity (Strober et al., 2020). Patients are candidates for a topical treatment or candidates for systemic treatment. They are candidates for systemic treatment when they have psoriasis over more that 10% of the body surface, have psoriasis at difficult locations, or have failed to show improvement through topical treatments. The use of this definition in clinical practice and future clinical trials will contribute to a better access of care and better alignment of clinical trial populations with real clinical practice.

From clinical practice, we know that early active intervention is needed to prevent stigmatization and help patients with psoriasis to lead a better life. An important question is: Does active early intervention improve the long-term course, and can we prevent comorbidities from occurring? Currently, there is an ongoing early intervention study on the long-term efficacy and safety of secukinumab, which is investigating the long-term effect of intervention within six months after the onset of psoriasis (Iversen et al., 2018).

In general patients who start and continue biologics for many years, “drug survival” is a commonly accepted parameter for the success of treatment. Can we develop a long-term treatment paradigm comprising dose reduction and treatment discontinuation? Few studies have been carried out on the development of long-term treatment paradigms. Recently, results from clinical trials have become available, which inform us on the course of the disease during 6–12 months after treatment discontinuation. Data on true disease modification are crucial to develop treatment paradigms for long-term disease control.

In current drug development programs for moderate to severe psoriasis, only patients with an objective severity of at least PASI 10 are included. It is borne out of clinical practice that many patients with a PASI below 10 require the medications for severe disease for severe impairment of quality of life, localization of psoriasis at difficult sites, severe itch, comorbidities, or risk factors for comorbidities, among other factors. Can we realize a better alignment of randomized double-blind controlled trials to real clinical practice? In future clinical trials, it is important to incorporate the patient-reported outcomes to capture the assessment of lesions at difficult localizations and assess comorbidities in order to have a personalized approach in treatment selection. Another question is: Can biomarkers be developed in clinical trial programs as codiagnostics to predict the treatment responses? Codiagnostic biomarkers may predict which patients are at a greater risk of developing serious disease over time and need innovative and more expensive treatments for that reason. In this respect, it is of importance to take advantage of the clinical data and responses to biomarkers that are already existing from the drug development programs.

A host of factors are relevant for treatment decision in real clinical practice. Analyses of these factors in registry data and combination with biobank data help to predict the course of the disease and treatment response. Health care is developing in the perspective of “computational medicine,” “precision medicine,” and “P4 medicine: predictive, personalized, preventive, participatory” (Sagner et al., 2017). Can an integrated application of biomarkers, clinical characteristics, and lifestyle information predict which treatment a patient has to initiate and when to stop the treatment? Analyses of the patient’s journey in these registries/biobanks can identify the relevant disease-modifying factors from the multitude of registered data. Registries and biobanks have to be very large to permit big data analytics.

Robust joint collaborations of international study consortia of academic centers and pharmaceutical industries
are crucial for making progress in the personalized medicine in psoriasis. Important examples of these consortia are the large patient registries such as Psoriasis Longitudinal Assessment and Registry (Friedman, 2020) and the program Biomarkers on Atopic Dermatitis and Psoriasis, which is a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (BIOMAP, 2019). Another example of a consortium with collaboration of academic centers and pharma industry is Psoriasis Stratification to Optimize Relevant Therapy, which investigates P4 therapies targeting the interleukin (IL)-23/IL-17 immune axis for the treatment of moderate-to-severe plaque psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2020;34:30–8.


