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EDITORIAL

Blueprint for mechanistic, data-rich early phase clinical pharmacology studies in dermatology

Numerous new and innovative drugs are currently entering the dermatological market space. The dermatologist of the 20th century used to have a limited amount of pharmacological treatment options comprising mainly nonspecific drugs such as (topical) corticosteroids and methotrexate. This has changed tremendously in the last two decades when novel, targeted therapies became the new hallmark for the treatment of moderate to severe skin diseases. Risankizumab, for instance, is a monoclonal antibody selectively targeting interleukin 23 in chronic plaque psoriasis and is the 12th unique biologic drug that is registered in Europe and in the United States. Having these multiple, targeted treatment options available has greatly improved the flexibility and personalization of psoriasis care in clinical practice. However, such targeted treatment options are still under development for various other indications including atopic dermatitis, chronic urticaria, hidradenitis suppurativa, vitiligo, and alopecia areata.

By definition, the early exploratory phase in clinical drug development is performed without clinical information on the drug, e.g., unknown active dose, unclear regimen, and uncertain pharmacological activity. This uncertainty leads to a probability of success as low as 13.8% from phase 1 to market registration across all therapeutic areas and 6.3% for auto-immune/inflammation treatments in particular.¹ Therefore, more rational approaches for drug development are needed such as question-based drug development with biomarkers included² or the quantitative model-based approach.² However, there is no clear guidance on how to perform early phase clinical trials with innovative topical or systemic drugs at the cross-road of dermatology and clinical pharmacology. Hence, with this editorial, we aim to illustrate the various aspects of recent examples to enable rational dermatological drug development for mostly nonmalignant skin diseases in the early clinical phase, i.e., human pharmacology and exploratory therapeutic setting. Importantly, biomarkers and drug development tools described in this manuscript need to be qualified or validated to enable reliability of the observations as described in more detail in the FDA guidances.^{3,4}

1 | CORNERSTONE: PHARMACOKINETIC PROPERTIES

One of the main aims in early phase clinical pharmacology studies is to explore the pharmacokinetic (PK) properties of the new drug. While PK profiling is rather easy for systemic compounds, it is more complicated for topical drugs, because of the investigation of drug concentrations in skin. Profiling of dermal PK poses an immense challenge for clinical pharmacologists, both for the topical and systemic route of administration. However, major advancements have been made using methods including microdialysis⁵ and the more recent open-flow microperfusion.⁶ Lately, the FDA has officially recognized the latter technique as a valuable tool to evaluate dermal PK of new drugs.⁷ In addition, more invasive techniques comprise mass spectrometry-based imaging from skin punch biopsies. The latter triggers more attention since matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) imaging techniques have become more established, enabling profiling of quantitative skin distribution.⁸ An interesting alternative for dermal PK assessments is the noninvasive confocal Raman spectroscopy whereby the first validation results hold promise to wider application and quantification *in vivo*.^{9,10} We should also note the rapidly expanding field of minimally invasive techniques for systemic PK profiling, including the only recently reported dry blood spot analysis for biologics (e.g., infliximab and adalimumab).^{11,12} While the most suitable technique needs to be selected on a case-by-case basis, the growing number of technical possibilities is encouraging, enabling the more precise assessment of dermal pharmacokinetics in future human pharmacology studies.

2 | CORNERSTONE: PHARMACODYNAMIC PROPERTIES

Next to PK and safety/tolerability profiling, early phase clinical pharmacology studies also should include the evaluation of

disease severity more objectively in atopic dermatitis the digital eczema area and severity index (EASIdig) demonstrated good correlation to clinical scores²³ and even more accurate assessments using artificial intelligence are currently being developed. Alternatively, the use of a combination of serum biomarkers may be a more objective tool for the assessment of clinical scores and drug effects in patients with atopic dermatitis.²⁴ For (benign) skin neoplasia such as cutaneous warts, three-dimensional (3D) imaging offers the opportunity to both accurately and precisely quantify lesions in terms of planimetry as well as high-resolution photo documentation²⁵ next to the morphological clinical assessment.²⁶ All imaging and biomarker techniques illustrate a more objective approach supporting well-informed decision-making during the process of drug development.

4 | CORNERSTONE: INTEGRATED, MULTIMODAL PROFILING OF DISEASE AND DRUG EFFECTS

The technological revolution of the last 20 years has had a major impact on clinical research. A rapidly growing list of tools is currently available for the comprehensive characterization of drug effects in the individual patient. Tools can be classified into different domains, including patient-reported outcomes, the classical physician-based clinical scoring, and biophysical, cellular, and molecular biological biomarkers as well as (pharmac)genomics and the external exposome. Various techniques can be employed, including transcriptomics, proteomics, lipidomics, and metabolomics as well as microbiomics (recently reviewed in Niemeyer-van der Kolk et al.²⁷ for dermatological drug development). By integrating this data from different domains, assessed by multiple techniques, we follow a so-called “systems dermatology” approach, describing the pathophysiology in high detail and supporting a holistic view on skin disease and drug effects (Figure 1). As a consequence, response or nonresponse to drugs can be elucidated and explained in more mechanistic detail. Finally, integration is needed of the holistic construct of the individual patient and real-world data captured at home for different symptoms such as itch, sleeplessness, and erythema as well as monitoring and controlling of treatment adherence. Recently, a meta-analysis of data from 6 different trials with topical drug application in 258 participating patients for various dermatological indications showed a mean treatment adherence of 98%, which is encouraging.²⁸ A noteworthy addition to this is the deep phenotyping of patients, often conducted in an observational study design prior to a clinical trial to characterize the disease, patient population, biomarkers, and associated endpoints most suitable to target.

5 | CORNERSTONE: LANDSCAPE FOR TRIAL CONDUCT: COLLABORATIONS

A “catalyzing” landscape for clinical trials is an essential extrinsic factor needed for efficient drug research, in addition to earlier described four

cornerstones on “intrinsic clinical trial factors.” Due to the complexity of modern clinical trials, a multidisciplinary setup is required involving various specialists such as technicians, bioinformaticians, dermatologists, key opinion leaders, and research physicians. All specialists and patients need to collaborate seamlessly while trial infrastructure and all associated procedures are fully aligned according to the standards of Good Clinical Practice. The most important critical aspect remains the efficient and effective identification and recruitment of suitable patients in clinical trials, which requires strong collaborative efforts and teamwork within the dermatological community. For this reason, active communities have been formalized in two different European countries: the UK Dermatology Clinical Trial Network (UKDCTN)²⁹ and the Dutch Clinical Network for Trials in Dermatology, called CONNECTED.³⁰ Through trial prioritization and complementary activities, these networks will flourish in trial execution, which has mutual benefits for each participating site and their patients. As for the Dutch CONNECTED network, physicians can provide input about study design, refer potentially eligible patients, and have timely access to the results of recently completed studies. Through multicenter recruitment, also mid-size proof-of-concept trials can be performed in a single center with up to 46 patients with moderate to severe psoriasis³¹ or 80 patients with cutaneous warts in a timely manner.³² Obvious advantages are the centralization of logistics, large samples sizes, high-data quality, and consistency as well as lower costs for the startup of one study site (versus multiple sites). Hence, this single-center approach with multisite recruitment marks the way-to-go for efficient and method-rich early clinical trials in the future.

In summary, these five cornerstones describe the most important aspects of a blueprint for early phase clinical pharmacology studies in the field of clinical pharmacodermatology. Each new drug needs a new tailored approach towards drug development. Taking into account the mentioned aspects will increase the probability that undesired drug features (in terms of safety, pharmacokinetics, or pharmacodynamics) are detected early in the clinical development process and mitigate the risk of drug failing in pivotal trials.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

R.R., M.v.D., and M.M. designed, wrote, and reviewed this editorial jointly. All coauthors approved the final version of the manuscript.

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