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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 included[2] 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 microdialysis[5] 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

pharmacodynamic effects of a new drug, as was recently re-emphasized by the EMA guidance on first-in-human clinical trials.[13] Pharmacodynamic properties can be investigated at the level of receptor occupancy in the target tissue and engagement of the target, assessed by proximal or distal functional downstream biomarkers to monitor target modulation.[14] Given the fact that most dermatological drugs have an immunomodulatory mechanism of action, translational models are of particular interest for human pharmacology. Such studies include in vivo or ex vivo immune challenges targeting innate immunity pathways, e.g., lipopolysaccharide for Toll-like receptor (TLR)-4 and imiquimod for TLR-7 stimulation, or adaptive pathways, e.g., the neoantigen keyhole limpet hemocyanin driving an antigen-specific T-cell and B-cell response.[15,16] Other valuable models include histamine or capsaicin challenges via skin prick, as model for pruritus as was reviewed by Assil et al.[17] Combining a dose-ranging trial with a proof-of-pharmacology trial at the earliest clinical stage (i.e., in healthy volunteers) results in proving the pharmacological action and supports rational dose selection for a subsequent "proof-of-concept" trial in a relevant patient population. Of note, for topical drugs, the healthy volunteer part can often be minimized or omitted, and the assessments can be performed directly in the relevant patient population. This approach can be more advantageous since it enables direct investigations in presence of disease pathology in a "first-*on*-human" study. Proven examples are the psoriasis plaque test[18] and the micro-zone models for atopic dermatitis[19] whereby pharmacological properties could be explored in parallel with clinical efficacy of the drug.

3 | CORNERSTONE: SENSITIVE AND OBJECTIVE CLINICAL ENDPOINTS

In pivotal dermatology trials, physician-evaluated scores play a key role in the assessment of drug efficacy. These symptom-grading scales, such as the Investigator Global Assessment (IGA) or Physician Global Assessment (PGA), can give a crude estimation of the disease "severity" and potential improvement during the clinical trial. These assessments are routinely performed and standardized, as is explicitly demanded by the regulatory agencies. However, their obvious disadvantages are (i) limited objectivity since the physician performing the assessment might introduce a response quantification bias, (ii) potential inter-rater variability, and (iii) lack of sensitivity that is needed to quantify smaller effects of a novel drug which are highly likely to occur in early phase clinical studies. Therefore, more objective endpoints are needed to support unbiased objective evaluation of drug efficacy. The amount novel techniques have expanded, providing many new endpoints currently postulated as value-based endpoints.[20] For example, in the evaluation of new drugs for the treatment of chronic plaque psoriasis, the PGA along with the Psoriasis Area Severity Index (PASI) are currently the gold standard assessments. Novel imaging techniques now additionally provide the digital PASI[21] as well as objective image quantification of an inflammatory skin lesion using Laser Speckle Contrast Imaging.[16] By measuring the perfusion of the lesion, the latter technique can objectively measure the inflammatory status of a psoriasis plaque and thereby potential drug effects. For other skin diseases including hidradenitis suppurativa mobile and automated tools are available to determine erythema.[22] To assess

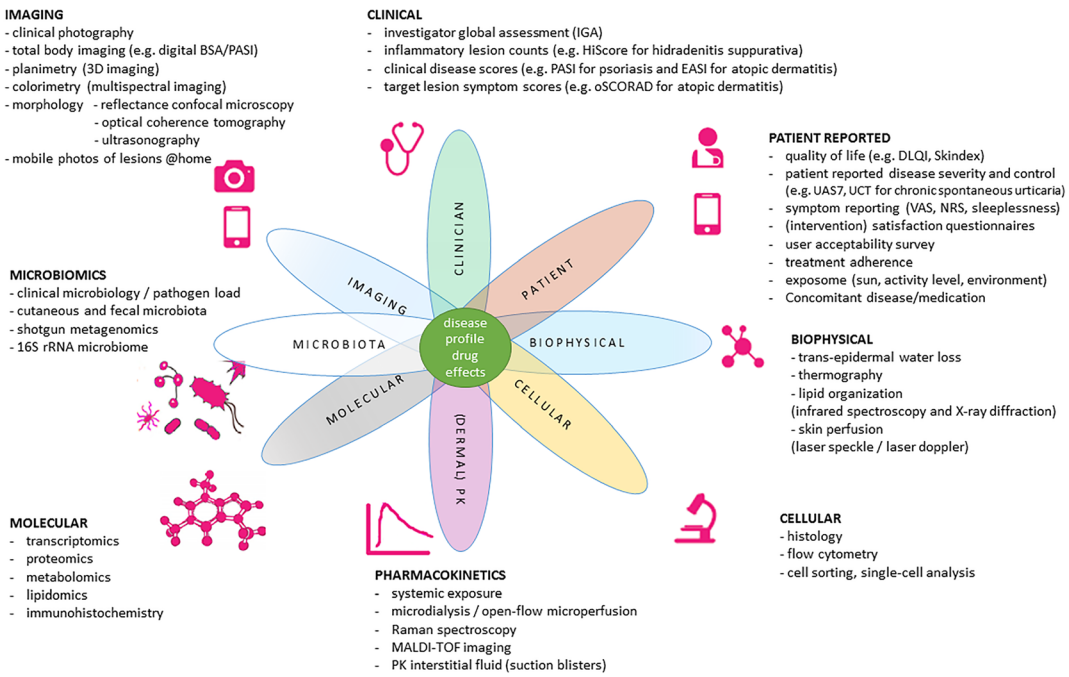

FIGURE 1 Sytems dermatology profiling of disease and drug effects needs a multi-modal approach with different technologies. BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; MALDI-TOF MS, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry; oSCORAD, objective scoring atopic dermatitis; NRS, numerical rating score; PASI, psoriasis area and severity index; UAS7, urticaria activity score; UCT, urticaria control test; VAS, visual analogue scale

disease severity more objectively in atopic dermatitis the digital eczema area and severity index (EASIdig) demonstrated good correlation to clinical scores[23] 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 documentation[25] 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 (pharmaco)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 psoriasis[31] 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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REFERENCES

1. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;20(2):273-286.
2. Cohen AF, Burggraaf J, van Gerven JMA, Moerland M, Groeneveld GJ. The use of biomarkers in human pharmacology (phase I) studies. *Annu Rev Pharmacol*. 2015;55:55-74.
3. FDA. Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff DRAFT GUIDANCE. 2018.
4. FDA. Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff. DRAFT GUIDANCE. 2019.
5. Pal A, Matzneller P, Gautam A, et al. Target site pharmacokinetics of doxycycline for rosacea in healthy volunteers is independent of the food effect. *Br J Clin Pharmacol*. 2018;84(11):2625-2633.
6. Dragatin C, Polus F, Bodenlenz M, et al. Secukinumab distributes into dermal interstitial fluid of psoriasis patients as demonstrated by open flow microperfusion. *Exp Dermatol*. 2016;25(2):157-159.
7. FDA. 2019 Available from: https://www.fda.gov/drugs/regulatory-science-action/impact-story-developing-new-ways-evaluate-bioequivalence-topical-drugs
8. Bonnel D, Legouffe R, Eriksson AH, et al. MALDI imaging facilitates new topical drug development process by determining quantitative skin distribution profiles. *Anal Bioanal Chem*. 2018;410(11):2815-2828.
9. Mateus R, Abdalghafor H, Oliveira G, Hadgraft J, Lane ME. A new paradigm in dermatopharmacokinetics—confocal Raman spectroscopy. *Int J Pharm*. 2013;444(1–2):106-108.
10. Caspers PJ, Nico C, Bakker Schut TC, et al. Method to quantify the in vivo skin penetration of topically applied materials based on confocal Raman spectroscopy. *Translat Biophoton*. 2019;1(1–2):e201900004.
11. Berends SE, D'Haens G, Schaap T, et al. Dried blood samples can support monitoring of infliximab concentrations in patients with inflammatory bowel disease: a clinical validation. *Br J Clin Pharmacol*. 2019;85(7):1544-1551.
12. Kneepkens EL, Pouw MF, Wolbink GJ, et al. Dried blood spots from finger prick facilitate therapeutic drug monitoring of adalimumab and anti-adalimumab in patients with inflammatory diseases. *Br J Clin Pharmacol*. 2017;83(11):2474-2484.
13. EMA. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1), July 2017.
14. Rissmann R, Szabadi E. Spotlight commentary: how to prove pharmacology of immunomodulatory drugs in a phase 1 trial? *Br J Clin Pharmacol*. 2019;85(7):1389-1390.
15. Niemeyer–van der Kolk T, van der Wall H, Hogendoorn G, Rijneveld RSL, van Alewijk D, et al. Omiganan enhances imiquimod-induced inflammatory responses in skin of healthy volunteers. *Clin Transl Sci*. 2020. https://doi.org/10.1111/cts.12741
16. van der Kolk T, Assil S, Rijneveld R, et al. Comprehensive, multimodal characterization of an imiquimod-induced human skin inflammation model for drug development. *Clin Transl Sci*. 2018;11(6):607-615.
17. Assil A, Rissmann R, van Doorn MBA. Pharmacological challenge models in clinical drug developmental programs. In: *Bookchapter of Translational Studies on Inflammation*. London, UK: Intech Open. 2019. https://doi.org/10.5772/intechopen.85352
18. Kang EG, Wu S, Gupta A, et al. A phase I randomized controlled trial to evaluate safety and clinical effect of topically applied GSK2981278 ointment in a psoriasis plaque test. *Br J Dermatol*. 2018;178(6):1427-1429.
19. Guttman-Yassky E, Ungar B, Malik K, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2017;140(4):1032-1042. e13
20. Kruizinga MD, Stuurman FE, Groeneveld GJ, Cohen AF. The future of clinical trial design: the transition from hard endpoints to value-based endpoints. *Handb Exp Pharmacol*. 2019;260:371-397.
21. Fink C, Fuchs T, Enk A, Haenssle HA. Design of an algorithm for automated, computer-guided PASI measurements by digital image analysis. *J Med Syst*. 2018;42(12):248.
22. Wiala A, Schollhammer M, Singh S, Rappersberger K, Schnidar H, Posch C. Digital assessment of hidradenitis suppurativa disease activity. *J Invest Dermatol*. 2018;138(5):S92-S.
23. Tremp M, Knafla I, Burg G, Wuthrich B, Schmid-Grendelmeier P. 'EASIdig'—a digital tool to document disease activity in atopic dermatitis. *Dermatology*. 2011;223(1):68-73.
24. Thijs JL, Drylewicz J, Fiechter R, et al. EASI p-EASI: utilizing a combination of serum biomarkers offers an objective measurement tool for disease severity in atopic dermatitis patients. *J Allergy Clin Immunol*. 2017;140(6):1703-1705.
25. Rijsbergen M, Pagan L, Niemeyer–van der Kolk T, et al. Stereophotogrammetric three-dimensional photography is an accurate and precise planimetric method for the clinical visualization and quantification of human papilloma virus-induced skin lesions. *J Eur Acad Dermatol Venereol*. 2019;33(8):1506-1512. https://doi.org/10.1111/jdv.15474
26. Hogendoorn GK, Bruggink SC, Hermans KE, et al. Developing and validating the cutaneous WARTS (CWARTS) diagnostic tool: a novel clinical assessment and classification system for cutaneous warts. *Brit J Dermatol*. 2018;178(2):527-534.
27. Niemeyer-van der Kolk T, van der Wall HEC, Balmforth C, Van Doorn MBA, Rissmann R. A systematic literature review of the human skin microbiome as biomarker for dermatological drug development. *Br J Clin Pharmacol*. 2018;84(10):2178-2193.
28. Rijsbergen M, Niemeyer–van der Kolk T, Rijneveld R, et al. Mobile e-diary application facilitates the monitoring of patient-reported outcomes and a high treatment adherence for clinical trials in dermatology. *J Eur Acad Dermatol Venereol*. 2020;34(3):633-639. https://doi.org/10.1111/jdv.15872
29. Simpson R, Layfield C, Williams H. Collaborative clinician-led research networks. *Clin Med (Lond)*. 2014;14(6):691.
30. Available from: www.dermaconnected.nl.
31. Balak DM, van Doorn MB, Arbeit RD, et al. IMO-8400, a toll-like receptor 7, 8, and 9 antagonist, demonstrates clinical activity in a phase 2a, randomized, placebo-controlled trial in patients with moderate-to-severe plaque psoriasis. *Clin Immunol*. 2017;174:63-72.
32. Rijsbergen M, Niemeyer–van der Kolk T, Hogendoorn G, et al. A randomized controlled proof-of-concept trial of digoxin and furosemide in adults with cutaneous warts. *Br J Dermatol*. 2019;180(5):1058-1068.