Rubor, calor, tumor, dolor: objective assessments of inflammation

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SECTION IV

SUMMARY AND APPENDICES

CHAPTER VIII

GENERAL DISCUSSION

Well-informed decisions are needed in the earliest phase of dermatological drug development. Only 6.3% of the drugs targeting immunosuppressive and anti-inflammatory processes reaches market registration. Knowledge about the pharmacodynamic properties of a dermatological agent is essential to increase the probability of success from early-phase clinical trials to market registration in dermatology. Despite the increasing amount of early-stage drug trials incorporating pharmacodynamic endpoints, there seems to be a lack of understanding how to integrate pharmacodynamic outcomes into early-stage dermatological drug trials. There are success stories from investigations employing objective pharmacodynamic endpoints in both disease and challenge models, showing that integrating such endpoints during the initial clinical stages of drug development is feasible. This thesis investigates and advocates a more objective methodology, suggesting the integration of imaging techniques and precise biomarkers as pharmacodynamic endpoints in early-stage dermatology trials. However, this advocacy for pharmacodynamic endpoints in early-stage dermatology trials raised two main questions: how to evaluate pharmacodynamic endpoints in early-stage dermatology trials and which specific pharmacodynamic endpoints should be considered for evaluation.

As the predominant focus of studies in the earlier stages of drug development remains on healthy volunteers, challenge models are being unequivocally endorsed. The present thesis outlined how pharmacological and trauma-based derma-immunological challenges are developed and how objective pharmacodynamic endpoints are evaluated in early-stage trials in clinical pharmaco-dermatology. Two types of skin challenge models were explored: trauma-based derma-immunological challenges, wherein a physical intervention was applied on skin to provoke an immunologic and inflammatory response to mimic a dermatological disease (**section I**), and pharmacological skin challenges, wherein a pharmacological agent is administered to the skin (**section II**). These challenges were applied in five early-phase dermatological trials. Additionally, one clinical trial was initiated to set an example how to evaluate pharmacodynamic endpoints in a classical phase I feasibility and dosing study but without using a skin challenge model (**section III**). After outlining the outcomes of the clinical trials, the focus of this discussion is to address the queries raised in the introduction: how to evaluate pharmacodynamic endpoints in early-stage dermatology trials and which specific pharmacodynamic endpoints should be considered for evaluation. With this we try to contribute to answering the question which objective pharmacodynamic endpoints deserve consideration in early-phase clinical pharmacology trials in dermatology.

SUMMARY OF FINDINGS

SECTION I: PHARMACODYNAMICS OF TRAUMA-BASED DERMA-IMMUNOLOGICAL CHALLENGES

In **chapter 2**, we presented a cutaneous full-thickness wound model to test novel wound healing treatments. In this chapter, three- and four-mm full thickness punch biopsies were taken from the lower back of healthy volunteers and left to heal without intervention. We aimed to characterize physiological wound healing with a multimodal test battery consisting mainly of non-invasive methodologies in a healthy volunteer challenge model. We demonstrated for the first time that a test battery of non-invasive techniques can objectively monitor quantifiable changes over time of the distinct wound healing phases, that is phase II inflammation, phase III proliferation and phase IV remodeling, while excluding the hemostasis phase. Additionally, multiple parameters were integrated and visualized in a radar chart highlighting the most important parameters and most suitable biomarkers per phase. Key findings of this study were that clinical imaging was an objective read-out for wound healing assessments, and we were able to distinguish the distinct phases of wound healing by integrated, multidimensional data visualization. The developed wound healing model shows promise to be a valuable tool for the standardized testing of novel wound healing treatments.

In **chapter 3**, we presented a trauma-based model aimed at the characterization of epidermal wound healing; this model was however based on the principle of suction blistering. In this chapter, we refined a previously developed suction blister model for analysis of suction blister fluid to monitor epidermal wound healing. This chapter illustrated for the first time that in our hands the blister method is suitable to monitor epidermal wound healing over time. We were able to induce blisters successfully and reproducibly with a clear separation of dermis and epidermis. The inflammation, proliferation, and remodeling phases were distinctly visible using objective pharmacodynamic biomarkers. We quantified several pharmacodynamic parameters, i.e., wound healing features, skin barrier function and skin perfusion via clinical imaging techniques, TEWL assessments and D-OCT. All parameters differed over time with comparable and acceptable variability. We were able to detect dermal structures with an emphasis on the separation of epidermis using D-OCT. Additionally, we could objectively measure the pharmacodynamic effects of a topical treatment alongside the blister suction model. Although the effects were limited, the techniques used to quantify the effects were sensitive enough to pick up differences over time.

SECTION II: PHARMACODYNAMICS OF PHARMACOLOGICAL CHALLENGES

Chapter 4 demonstrated a pharmacological model with substance P (SP). This chapter outlined the setup of an intradermal challenge model utilizing SP, a neuropeptide known to induce wheal and flare responses and serving as a potential challenging agent for investigating such responses mediated by the mas-related G-protein coupled receptor member X2 (MRGPRX2) receptor. Main objectives of this open-label, two-part, prospective enabling study in healthy volunteers were to assess the robustness of the SP response by evaluating the effect of varying doses of SP on wheal and flare, which are endpoints associated with MRGPRX2 receptor-mediated mast cell degranulation. Initially, a single challenge visit involving 20 healthy subjects aimed to determine the optimum dose range of SP for subsequent evaluation. Intradermal microdialysis (IDM) was employed to SP-challenged skin, involving the insertion of dialysis membranes into the dermis, which were then perfused at low rate with perfusate. This technique facilitated continuous sampling of interstitial fluid from SP-challenged skin, enabling assessment of the effect-time relationship. Subsequently, the effect of the selected dose of SP on wheal and flare responses, also assessed with IDM, was evaluated at two consecutive challenge visits. The time profile of the challenge for wheal and flare responses provided greater insight and characterization of the effect of multiple doses of SP over multiple timepoints, in addition to determining the potential carryover effect following repeated challenge. Lower doses of SP produced dose-dependent wheal and flare responses. Findings of this study support the fit-for-purpose validation for application of the challenge model in future clinical studies.

Chapter 5 described the effects of two novel, highly selective inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4), BAY1834845 (zabedosertib) and BAY1830839 or a control treatment ,i.e. prednisolone 20 mg or placebo, in human *in vivo* experimental challenge models of topical and systemic inflammation. The investigations conducted in this mechanistic clinical phase 1 study revealed that administering BAY1834845 (zabedosertib) at 120 mg B.i.d. and BAY1830839 at 100 mg B.I.D. for 7 days resulted in a rapid and distinct anti-inflammatory effect in a human skin challenge model with IMQ, as well as in a human systemic LPS challenge model. Both the topical IMQ challenge and intravenous LPS challenge are clinically well-characterized models that have been utilized to demonstrate the pharmacological activity of candidate drugs. What sets this study apart is the combination of two already established models, highlighting the potential utility of concomitant use of various novel human pharmacological models for evaluating the immunomodulatory effects of anti-inflammatory molecules in early-stage drug development.

SECTION III: PHARMACODYNAMICS AT THE EARLIEST PHASE OF CLINICAL DRUG DEVELOPMENT: RELEVANCE FOR OPTIMIZING DRUG ADMINISTRATION

Subcutaneous injections of drugs have been perceived as unpleasant and painful, especially during long-term use in both adults and children. **Chapter 6** explored the impact of repeated methotrexate injections via microneedles in children. This chapter presented the findings of a systematically performed literature review focused on children undergoing treatment with disease-modifying anti-rheumatic drugs (DMARDS). Insights from this review hold significance due to the perceived high treatment burden and the development of needle phobia among children with rheumatic diseases, which may affect long-term treatment adherence. The review identified two relevant studies involving children with juvenile idiopathic arthritis (JIA) receiving methotrexate. These studies indicated that needle fear, the effect of methotrexate treatment, and procedural consequences, such as blood sampling, all contribute to the distress and reduced quality of life among children with JIA. Notably, no studies investigating fear of injections or injection-related pain in children with rheumatic diseases receiving biologicals were found. This study emphasizes the importance of systematically exploring needle fear to optimize the administration of DMARDS, thus laying the groundwork for the setup of a prospective placebo-controlled trial outlined in the subsequent chapter of this thesis.

Chapter 7 detailed the establishment of a single-center double-blind, placebo-controlled, double-dummy clinical trial aimed at addressing the safety and efficacy of using hollow microneedles to administer a model monoclonal antibody (MAB). This chapter describes the feasibility of the intradermal administration of adalimumab via hollow microneedles versus conventional needles, evaluating their effects on pain, acceptability, local tolerability, pharmacokinetics, and immunogenicity. Conducted among 24 healthy adults, this trial compared the intradermal administration of 40 mg adalimumab (0.4 mL) using a hollow microneedle with subcutaneous administration using a conventional needle. Intradermal administration of biopharmaceuticals through hollow microneedles is suggested as an alternative for subcutaneous injection due to reduced injection-related pain and potentially more favorable pharmacokinetics compared to subcutaneous administration. Additionally, the applicability of optical coherence tomography, clinical photography, thermal imaging, and laser speckle contrast imaging in assessing skin reactions following intradermal injections was explored. In vitro protein analysis was performed to evaluate the compatibility of adalimumab with the hollow microneedle device. Intradermal injection of adalimumab via hollowing microneedles was found to be more painful and less accepted than subcutaneous administration, but

higher relative bioavailability with comparable safety and pharmacodynamic effects were found.

CHALLENGE MODELS IN EARLY-STAGE DERMATOLOGICAL DRUG DEVELOPMENT

Challenge models serve as invaluable tools for drug developers, enabling the replication of physiological and pathophysiological processes associated with inflammatory skin diseases. Initially, the focus of this thesis was on delineating two clinical trials with trauma-based challenge models: a cutaneous full-thickness wound model to test novel wound healing treatments and a model based on the principle of suction blistering. The wound healing models described and scrutinized in the clinical trials explained upon in **chapters 2** and **3** characterize pioneering research, using an explorative approach. Findings reveal that the most obvious challenge in trauma-based skin challenges lies in the uncertainty surrounding the time course of assessments. Balancing the inclusion of a comprehensive assessment scheme, which yields rich data, with the reasonable burden it places on participants, proves to be a pivotal consideration. Presently, information regarding the appropriate timing of assessments relies on preclinical studies, often conducted in animal models or in vitro models.[1] Regrettably, literature pertaining to early-phase studies incorporating trauma-based challenge models offers scant insights into the temporal aspect of assessments, typically reporting only the time to closure. Consequently, intriguing disparities observed over time, such as those between TGF-β1 and TGF-β3 discussed in **chapter 2,** present challenges in interpretation. These growth factors, integral to both inflammation and proliferation phases, are thought to activate similar intracellular signaling pathways.[2,3] Nonetheless, discrepancies in the elevations of TGF-β1 and TGF-β3 appear discordant, posing complexities in understanding their respective roles within the context of derma-immunological challenges. These complexities also relate to the interpretation of unexpected outcomes, e.g., that IL-6 would consistently yield zero values in the QPCR analysis in a normal wound healing model devoid of intervention, which again might be due to the sampling rate. The deconstruction of physiological processes into discrete components through modeling constitutes a fundamental aspect of research. Consequently, understanding the time course of events in multiple scenarios, e.g., diseased skin versus healthy skin, full-thickness versus scratch wounds, will furnish us with insights into the underlying mechanisms of wound healing.

The establishment of a suction blistering model in **chapter 3** represents an initial stride toward devising an epidermal wound model in healthy volunteers incorporating multiple non-invasive measurements. However, a remaining issue is the fidelity of the blisters generated in this model to those characteristic of epidermolysis bullosa (EB) and other bullous diseases. By introducing acute trauma, we bypass a normally longer process (days/weeks versus 1.5 hours) which might elicit an immune response different from chronic disease states.[4] Additionally, insights gathered from this challenge model confronted us with an apparent ambiguity. Notably, tissue inhibitors of metalloproteinases (TIMPS) increased directly post-wounding yet reverted to baseline levels more swiftly compared to matrix metalloproteinase-9 (MMP-9), the latter of which displayed a continued escalation until day 4. As future investigations unfold, including analogous blister suctioning models, we anticipate an increased understanding of the timing and implications of these findings as well as an integrated analysis as performed for the full-thickness wounds.

Conversely, a more extensive body of knowledge exists regarding the time course of assessments within trials including pharmacological challenge models. **Chapter 4** highlighted a pharmacological model employing substance P (SP), while **chapter 5** delineated a human skin challenge model integrating topical IMQ and systemic LPS to elucidate the effects of a candidate IRAK4-inhibitor. Notably, the combined IMQ/LPS challenge model, deployed for the first time in a clinical trial together with novel IRAK4 inhibitors, proved to be groundbreaking. This innovation enabled the differentiation of local and systemic challenge effects, affirming the feasibility of this model in healthy volunteers. **Chapter 4** provided support for the utility of the SP model. Despite the existence of dose-dependent data on SP effects, a comprehensive characterization and insights into potential carryover effects following repeated challenges were lacking. Nevertheless, data revealed the absence of a carryover effect when the challenge was repeated after a 2-week interval. This study was a testimony to the continuous development of challenge models since each new study contributes to knowledge about the model.

In summary, the selection of a specific pharmacological skin challenge in early-phase clinical trials appears contingent upon the underlying research question. Such skin challenges supply proof-of-mechanism in early-phase clinical trials, while including safety and pharmacokinetic parameters, and insights into dose escalation based on pharmacodynamic measures. Nonetheless, the presence of model limitations, such as an unknown time course of assessments, precludes the provision of conclusive evidence for a direct translation into clinical efficacy, particularly in studies including trauma-based challenge models.

PHARMACODYNAMIC ENDPOINTS IN EARLY-STAGE DERMATOLOGICAL DRUG DEVELOPMENT

This thesis advocates a more objective approach that incorporates imaging techniques and accurate as well as precise biomarkers as pharmacodynamic endpoints in early-stage dermatology trials. While outcomes reported by physicians and patients offer clinically relevant information and can be integrated into routine dermatologic practice and pivotal phase 3 dermatology trials, their applicability in early-stage trials is limited. This thesis bundles 5 randomized controlled trials wherein the most appropriate objective pharmacodynamic outcome measures were chosen, and several non-invasive (imaging) tools were successfully applied to detect biomarkers. The challenge remains in identifying biomarkers accurate enough to make critical go/no-go decisions in early-stage dermatology trials. Ideally, a parametric and accurate biomarker of the pharmacological influence of a critical pathophysiological process is available to reflect the pharmacodynamic effect of a therapeutic agent. Thorough generation of data and experience in biomarker studies are therefore warranted. This thesis highlights many imaging techniques, such as stereophotogrammetry, multispectral imaging, optical coherence tomography (OCT), laser speckle contrast imaging (LSCI) and transepidermal water loss (TEWL). Additionally, it mentions more standard techniques (e.g., QPCR and HE biopsy staining) that are not within the scope of this discussion. While providing insight into the intricate interplay of physiological processes in human skin, including inflammation, immune responses, wound healing, and angiogenesis, not all techniques are readily applicable biomarkers *yet*. In general, LSCI proved to be a highly reliable and easy to execute technique. The inter-subject variability was acceptable allowing to detect treatment and challenge effects. In our hands, OCT proved to be an especially useful qualitative tool but lacked consistency in calculating automated quantitative parameters. Despite its rapidity, simplicity, compactness, and cost-effectiveness, OCT had some limitations that became obvious in **chapter 2**. Although OCT was an objective read-out for wound healing assessments in this study, it did not have the diagnostic power and resolution needed to detect all wound healing processes and small microenvironmental changes which, currently, could only be assessed using histology. Its spatial resolution might have been troubled by the so-called resolution-penetration depth paradox, i.e., imaging deeper tissues generates visuals with poor resolution and imaging superficial cells generates visuals with relatively good resolution.[5] The resolution of OCT is between the very good spatial resolution of confocal microscopy, which only detects cells without tissue penetration, and the resolution of ultrasound that visualizes tissue lower than the dermis but is unable to detect individual cells. While OCT can detect significant structures within the dermis, it lacks the specificity required to distinguish between diseases effectively. In addition, OCT required trained operators to reduce the number of artefacts in scans. In addition, TEWL is known to be subject to numerous environmental and individual variables, such as age, gender, ethnicity, anatomical location, skin temperature, external surroundings, seasonal variations, smoking habits, and measurement tools.[6,7] Consequently, establishing a definitive 'normal' TEWL value and determining thresholds indicating pathological significance remain topics of ongoing debate.

Based on the findings presented in this thesis, it can be concluded that some techniques (TEWL, LSCI and multispectral imaging) are currently more suited for implementation as objective endpoints than others (OCT). However, ongoing advancements in imaging and detection techniques show promise in improving resolution while maintaining imaging depth. Examples include line-field optical coherence tomography and reflectance confocal microscopy.[8,9] Line-field confocal optical coherence tomography (LC-OCT) combines the principles of time-domain OCT and confocal microscopy, utilizing line illumination and detection with a broadband laser and a line-scan camera. With these developments, OCT or an advanced type of OCT could become a future biomarker in clinical drug development. In the near future, improved imaging techniques might be less-invasive alternatives for biopsies and staining that are still the gold standard in drug development and clinical practice. The challenge in developing a test battery of non-clinical imaging methodologies lies in identifying the most sensitive and representative endpoints and excluding endpoints with too much variability and noise. In exploratory research (as in this thesis), it is entirely feasible to include numerous endpoints. However, when exploratory endpoints become primary or secondary endpoints and underlie data-driven decisions, study designs should be lean and only include endpoints with sufficient sensitivity and reproducibility to be considered as reliable biomarkers.

MULTIMODAL PROFILING

Changes in parameters observed through imaging modalities or biomarker assessments are less relevant without accompanying clinical effects. Therefore, profiling the interplay of physiological processes in human skin in early-stage research should eventually incorporate multimodal parameters, including both physician-evaluated and patient-reported scores alongside imaging modalities and objective biomarkers. The blueprint of mechanistic dermatology trials using multiple readout angles as described earlier was developed to capture multimodality in early-stage clinical pharmacology studies by considering pharmacokinetic and pharmacodynamic properties of a new drug, and sensitive and objective endpoints from different domains.[10] Combining all

readouts provides a multifaceted overview of a dermatological condition, but also allows to gain insight into its pathophysiology and into the relationship between pathophysiology and clinical representation. Clinical endpoints are composed to assume a pivotal role in later-phase clinical trials. And although early-phase clinical trials are not inherently designed to directly assess clinical endpoints, insights into potential clinical efficacy are invaluable in the trajectory toward successful compound marketing. Evaluating clinical endpoints can also offer insights into the pathophysiology of dermatologic conditions, but most clinical efficacy scales show limited objectivity, inter-rater variability, and lack of sensitivity.[11–13]

A clinical composite score attempts to combine clinical parameters by averaging their individual scores (e.g., a score of erythema of 1, and oedema of 2 results in an EASI score average to 0.3 with an involvement of 1-9% of the skin).[14] Using clinical composite scores in advanced statistical modelling might not be the holy grail, as implementing composite scores into a multifaceted analysis including objective sensitive quantitative endpoints might reduce the sensitivity of the outcome. Considering that the expected effect and signal-to-noise ratio are small, clinical scores offer limited value in advanced statistical models.

The challenge lies in effectively interpreting the information from multiple endpoints to entirely profile disease progression, while ensuring attention to detail and monitoring individual parameter changes. This thesis outlines numerous (non-) invasive imaging methodologies employed to examine individual parameters. However, a shift in a single parameter does not necessarily equate to a change in clinical impact. As was illustrated in drug development, targeting a single protein or receptor believed to be responsible for disease symptoms does not always indicate clinical impact, which also accounts for imaging modalities and biomarkers that phenotype challenge effects. By integrating all parameters into domains and/or paradigms, and using this comprehensive approach to detect treatment effects, we may be better equipped to describe diseases and drug impacts in a more realistic manner. It should be noted however that incorporating multiple endpoints in a multifaceted analysis will result in small pieces of information on many parameters. Decisions about the relevance of each finding requires thoughtful interpretation of the results of preselection of the most relevant parameters to be included in a statistical model.

FUTURE DIRECTIONS

This thesis is built upon the assumption that assessing the pharmacodynamic properties of a dermatological agent could increase the probability of success from early phases to market registration in the field of pharmacological dermatology. Only 6.3% of the drugs targeting immunosuppressive and anti-inflammatory processes, reaches market registration. The results presented in this thesis point towards a more nuanced future perspective on how early-phase clinical trials with skin challenge models and with objective outcomes assessments could improve marketing success.

OPTIMIZING EARLY GO/NO-GO DECISIONS

As new compounds compete with standard of care and regulatory bodies demand greater evidence prior to market approval, drug development grows increasingly complex.[15] Combined with a more reluctant investment climate, there is a need for early indicators of efficacy to enhance the chances of success. Integrating objective and quantitative endpoints in derma-immunological trials provides crucial insights into a compound's performance at an early stage, aiding in making go/no-go decisions. While this does not necessarily translate to an increase in the 6.3% of drugs reaching the market, it could help to allocate less resources on ineffective compounds. Moreover, better dose rationale within patient populations, based on a pharmacodynamic approach to dose escalation, could potentially lead to increased approvals.

REDESIGNING EARLY-STAGE TRIALS

The IRAK4 study in **chapter 5** clearly illustrated how insights gained from biomarker assessments at an early stage could inform the redesign of subsequent clinical trials. This mechanistic clinical phase 1 study delineated a human skin challenge model integrating topical IMQ and systemic LPS to elucidate the effects of a candidate IRAK4 inhibitor. The results of this study helped drug developers differentiate a target indication and proceed to a subsequent phase 2 study with more knowledge about their compounds. Currently, a study is underway in atopic dermatitis with the candidate IRAK4 inhibitor tested in **chapter 5**. By utilizing these biomarker-heavy and mechanistic question-based development strategies, the indicated 6.3% market approval rate for all new compounds in immunological dermatology might be lifted to 13.8%.

EVOLVING TECHNOLOGY

Imaging techniques are continuously evolving. For instance, accurate erythema measurements with smartphones (ScarletRed)[16] are increasingly common, replacing the exclusive reliance on clinical scores. Imaging modalities employing non-visible light are also advancing, enhancing skin penetration while maintaining resolution.[9] Moreover, analysing capabilities of digital images are rapidly improving. Previously, algorithms were used to classify and annotate certain skin structures beneath the surface, but with the aid of artificial

intelligence and enhanced algorithms, this can be achieved without human intervention, leading to even higher specificity. These advancements promise to enhance image quality and quantitative analysis, thereby facilitating a better understanding of diseases and improving success rates.

THE IDEAL EARLY-STAGE CLINICAL TRIAL

Ideally, early-stage clinical trials in healthy volunteers should consistently incorporate relevant biomarkers. The era of exclusively focusing on safety and tolerability has passed and investors now demand more information regarding proof of concept as well.[17] This shift necessitates drug developers to prioritize target engagement from the outset, prompting drug testers to consider appropriate biomarkers to test new therapeutics. The selection of these biomarkers should be based on the most important question to answer for a compound. For instance, if literature and preclinical work indicate that dermal penetration of a compound is a challenge, dermal PK assessment becomes a valuable tool for evaluation. Similarly, if a novel technique like microneedles is used for compound delivery into the dermis, OCT or ultrasound are useful to detect fluid disposition in the dermal layer. Although quantitative readouts are crucial for comprehending the underlying mechanism, totally discarding clinical scores is unwarranted. The combination of objective readouts with subjective clinical scores facilitates understanding the correlation between the two and aids in translating proximal biomarkers (e.g., cytokine analysis) into clinical effects (e.g., itch or erythema).

OVERALL CONCLUSIONS

This thesis explored various skin challenge models that provoke immunologic and inflammatory responses and simulate dermatological diseases. Objective pharmacodynamic endpoints in clinical pharmaco-dermatology were evaluated across several early-stage dermatology trials, with some biomarkers proving useful and others not. The findings underscore the necessity of thorough validation and feasibility assessments for biomarkers before including them as primary or secondary endpoints in clinical trials. The 'trial and error' paradigm remains crucial for testing devices in clinical settings and identifying useful parameters. By examining diseases using these pharmacodynamic imaging tools, both with and without treatment, valuable insights are gained into disease pathology and drug effects. While the ideal of measuring effect with a single well-validated biomarker remains elusive in dermatology trials, combining multiple aspects of disease pathophysiology will be the focus for future dermatology research.

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