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Chapter

Pharmacological Challenge Models in Clinical Drug Developmental Programs

Salma Assil, Robert Rissmann and Martijn Bastiaan Adriaan van Doorn

Abstract

Early phase clinical research for drug development requires the investigation of safety, tolerability and efficacy of novel compounds. The latter is hampered by the absence of the disorder in healthy volunteers, which is why challenge models are often applied in order to demonstrate ‘proof of pharmacology.’ These challenge models can often be translatable from animal work and can inform the drug developer which dose, dosing regimen or application frequency should be selected prior to phase II studies in the target population. Furthermore, these challenge models represent well-controlled settings to perform activity screening of the compound. The following skin challenge models will be reviewed in this chapter: inflammation induced by Toll-like receptor agonists such as imiquimod, KLH challenge, UV-B irradiation and histamine.

Keywords: skin inflammation, immune system, imiquimod, translational model, pruritus, drug development

1. Introduction

Drug development programs are well-established and long-lasting processes, taking between 10 and 15 years, from discovery to market availability. Clinical trials with drug candidates are the final stage in drug development programs [1, 2]. These clinical trials are often classified into four stages of experimentation, phase I—IV, which are used as a general guideline in clinical trial research for development of a new treatment in specific diseases, i.e., skin diseases [3]. In general, safety, tolerability and pharmacokinetic properties are assessed in healthy volunteers during phase I. The candidate drug will move on to phase II when the initial safety and tolerability has been determined. The main aim of phase II is to establish the safety and efficacy of the drug in the target population. Phase III studies involve large-scaling testing to provide more and extended information on the effectiveness of the drug and on the benefits and possible adverse events. The last phase, IV, also known as the post marketing surveillance trials, is executed after the drug enters the market. The main purpose of this monitoring phase is to determine the long-term effectiveness and patient’s quality of life and cost-effectiveness [4, 5].

Translational research focuses on the transcription of the animal model into humans, also known as first-in-human-dose. In general, efficacy, safety and tolerability are examined in the early phases of clinical research. However, the absence
Translational Studies on Inflammation

of the disorder in healthy volunteers may hamper investigation of the above-mentioned hallmarks of drug development. Inflammation, for example, plays an important role in diseases and is often an indication for a certain skin disease. Difficulties occur when testing drugs against inflammation in volunteers who do not have this condition. Therefore, pharmacological challenge models have been established to mimic physiological and pathophysiological conditions of several skin diseases. These models distort the physiological condition and lead to temporary effects that mimic the pathophysiology of the disease.

Table 1 gives an overview of established skin challenge models.

This approach includes translating basic scientific discoveries into clinical applications. Several recent developments in plaque psoriasis are noteworthy, which serve as an example of research with many translational aspects [42, 43]. Psoriasis is a chronic, inflammatory skin disease that is characterized by erythematous, itchy plaques covered by course scales on the extensor surface of the elbows and knees, as well as the scalp, dorsal hands and lumbar area. Also, the nails and joints (psoriatic arthritis) can be affected [44, 45]. Psoriasis is a multifactorial disease but the

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BCG: Bacillus Calmette-Guérin; LPS challenge: lipopolysaccharide; injected UV killed E. coli: Injected ultraviolet killed Escherichia coli; KLH: keyhole limpet hemocyanin; UV-B: Ultraviolet B.

Table 1. Overview of human skin challenge models.
hallmarks of pathophysiological pathways (Th1/Th17) with interleukin-12/23 and IL-17 have been clearly established as most important players. Over the last decade many new compounds have been in development for psoriasis yielding a total of 11 registered, targeted monoclonal antibodies today. In these drug development programs in vivo models in mice are of great importance for the setup of clinical programs. These mouse models needed to be made suitable to display certain features of psoriasis, since mice are unable to develop psoriasis themselves [10]. This research resulted in development of diverse mouse models i.e., spontaneous mutation model, genetically engineered model, cytokine injection model and transplantation model. All of the mentioned animal approaches represent more or less psoriasis-like cutaneous characteristics. Despite expression of psoriasis like features, the models also have some limitations including the need for special experimental facilities and lack of effectiveness of anti-psoriatic drugs [46–49]. In general, animal models are far from perfect especially in terms of pharmaco- and toxicokinetics.

Animals are not able to predict health effects in humans better than humans themselves. Monkeys reflects the human being the best, however, even they can differ as became clear in 2016. An anti-CD28 antibody caused multiple organ failures in six healthy volunteers within hours, despite multiple normal tests in monkeys. This shows that animal models may have limited predictability for safety in humans. Ethical concerns with regard to need for animal testing may also be a factor underlining the need for pharmacological challenge models in humans [50].

This chapter will provide a detailed overview of four different, local inflammation models: inflammation by Toll-like receptor agonists such as imiquimod (inflammation), UV-B irradiation (inflammation and pain), histamine provocation (itch) and KLH challenge (delayed type hypersensitivity).

2. Imiquimod skin inflammation model

Skin inflammation is a common response of our immune system to penetrating pathogens, skin trauma, exposure of xenobiotics, microbes and parasites [51–53]. Inflammation is clinically recognizable by erythema, pain, heat and swelling [54]. Generally, in inflamed skin, various immune cells, of both the innate and adaptive system are involved to combat the pathogens. However, imbalance of these immune cells may lead to chronic skin diseases such as psoriasis vulgaris, atopic dermatitis and acne vulgaris. Currently, many investigations are addressing the biomolecular mechanisms of inflammation; however, the pathophysiology of the skin remains complex and needs further investigation [55, 56].

Hence, various models in healthy volunteers were developed that mimic inflamed skin conditions [57]. One of the examples is the challenge model with topical application of imiquimod, the active ingredient of Aldara cream. Imiquimod is a small molecule with a low molecular weight and high lipophilicity which is preferable for absorption in the skin after topical administration. This small molecule is also a ligand for toll-like receptor seven and eight (TLR), which belongs to the class of immunomodulatory agents and is able to induce the production of several cytokines (interferon-1 response) with antiviral and tumoricidal properties. The mechanism of action of imiquimod is complex and three main pathways are required including TLR signaling, inflammasome activation and inhibition of the adenosine receptor. However, limited information is available on the mechanism of imiquimod on the adenosine receptor. The first pathway is TLR dependent and activates nuclear factor kappa B (NF-kB) signaling via My-D88, which is important in an early immune response. Herewith, activation of c-Junk and IRAK pathways occur which are involved in the production of several
pro-inflammatory cytokines. The second pathway is TLR independent. Imiquimod is able to activate the inflammasome via the NALP3 pathway, which also triggers an immune response and leads to production of interleukin-1β (IL-1β, a pro-inflammatory cytokine) [10, 11, 13, 58–60].

Aldara 5% cream is registered as a topical product that is indicated for the treatment of superficial basal cell carcinoma, actinic keratosis and genital and peri-anal warts (condyloma acuminata). Topical administration of imiquimod appears to be safe and reasonably tolerated according to the mouse model. This murine imiquimod challenge model has been widely used to examine the mechanisms involved in psoriasis vulgaris, since it is simple, inexpensive and develops an acute inflammatory response with psoriasiform features. However, in general, the main limitation of murine models is that no single mouse model is able to reflect human disease precisely, as the physiology and the pathophysiology of the skin differs in both species [61]. Therefore, recently, human studies been conducted that study skin inflammation after topical application of imiquimod.

Vinter et al. successfully developed an imiquimod-induced psoriasis-like skin inflammation model in humans by applying imiquimod topically under occlusion on non-lesional psoriatic skin of the lower back. A group of patients (n = 7) received the treatment and vehicle for 2 days, while the other group (n = 3) received the same treatment for 7 days. All the treatments were applied on tape stripped skin resulting in perturbation of the skin barrier. After 2 days of treatment with imiquimod, a significant upregulation in mRNA expression was observed for the pro-inflammatory cytokines tumor necrosis factor α (TNF-α), IL-1β and IL-6, whereas TNF-α and IL-6 are keratinocyte driven cytokines. Additionally, a high level of IFN-γ and IL-10 was found, the latter has an important role in suppression of the inflammatory response in the skin, as it influences the regulatory T-cells. In this model, inflammation and psoriasis-like characteristics were induced; however, typical psoriasis lesions were not observed and therefore appear to be the main limitation of the study.

A different approach to study skin inflammation was established by Van der Kolk et al. by applying imiquimod topically to healthy volunteers under occlusion. A distinction between the two groups was made. The first cohort received a topical treatment for 24, 48 and 72 hours on the intact skin barrier, while the second cohort received exactly the same treatment on a compromised skin barrier, through tape stripping (Figure 1). In this open label, dose-ranging study, erythema and blood perfusion were monitored by means of erythema index photo analysis, erythema colorimetry, erythema visual grading and laser speckle contrast imaging (LSCI). A dose-dependent increase in erythema was observed for all measurements, with a more rapid and pronounced effect in the tape stripped group. This model showed no clear differences in erythema intensity between the treatments after 48 and 72 hours, which is in concordance with observations in the murine model [9, 13]. Additionally, an increased skin perfusion was found after treatment with imiquimod, however this was only observed in the tape stripped cohort. A similar effect was found for the biomarkers in skin biopsies. Tape-stripping combined with imiquimod treatment resulted in an upregulation of gene expression of CXCL10, MX-A, ICAM-1 and hBD-2 after 48 and 72 hours. The same results were observed after treatment with imiquimod only compared to vehicle, however to a lesser extent. Imiquimod has a three-step mechanism, which entails an initial (24 hour), intermediate (24–72 hour) and late phase (>72 hour). In the intermediate phase of imiquimod, activation of both the innate and adaptive immune response takes place, which is characterized by infiltration of neutrophils, lymphocytes, and macrophages, based on the findings reported in the review of translational imiquimod skin inflammation.
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models [59]. In addition, histologically, infiltration of CD11+, HLA-DR, CD4+ and CD8+ into the dermis was observed. Increased infiltration was more pronounced in the tape stripped cohort, however, no differences were observed between 48 and 72 hours of treatment [9].

This chapter focuses mainly on translating skin inflammation into a model that can be used in healthy human volunteers. In the past decades, a lot of research has been performed in this field; however, murine models remained the gold standard. Since skin inflammation plays a crucial role in skin diseases such as psoriasis and atopic dermatitis, Vinter et al. established a human counterpart to the mouse model of imiquimod induced psoriasis like skin inflammation [13]. Despite the expression of different pro-inflammatory cytokines and the presence of psoriasis-like features, typical psoriasis lesions were not observed. However, this study formed the base to the inflammation model developed by Van der Kolk et al. where imiquimod has been applied under occlusion to challenge the skin. This model resulted in expression of certain cytokines and chemokines that are involved in activation of innate as well as adaptive immune system. Chemokines such as CXCL10 are expressed through activation of keratinocytes in inflamed skin. Expression of MX-A, a downstream interferon, which corresponds with the activation of plasmacytoid dendritic cells (pDCs), was also upregulated in the tape stripped cohort. The presence of interferons reflects the antiviral response, which is in concordance with the antiviral characteristics of imiquimod, used for HPV-induced diseases [62, 63]. Based on these findings, the murine imiquimod skin inflammation model was translated to a safe, human model in healthy volunteers. Skin erythema, skin perfusion and expression of cytokines had high intensity in the tape stripped cohort due to the enhanced transepidermal drug delivery. This model is suitable as a challenge model and can be used in drug developmental programs where TLR 7 is involved. Currently, several drugs are under development targeting TLR7/8 that have anti-tumor characteristics with more than 30 leads to be explored within the next years [64, 65].

Figure 1. Overview of the treatment schedule. (a) Treatment areas 1, 2 and 3 were treated with 5 mg imiquimod respectively for 24, 48 and 72 hours. All treatments were applied under occlusion by a 12 mm Finn chamber. (b) Clinical impression of site 3 of the tape stripped cohort after 72 hours of imiquimod treatment [9]. Permitted for non-profit use.
3. Models for itch: histamine and cowhage provocation

Itch, interchangeably used as pruritus, is a common skin sensation and together with pain are crucial symptoms in many chronic and allergic skin diseases. Itch can be induced by mechanical, thermal and chemical stimuli. Additionally, itch can lead to impairment of the skin and thereby affect a person’s quality of life. Yosipovitch et al. defined different types of pruritus that are involved in chronic itch including pruriceptive, neuropathic, neurogenic and psychogenic itch. Skin inflammation, dryness, or other skin damage are the main factors causing pruriceptive itch and are found in diseases such as scabies, urticaria and insect bite reactions [66, 67]. Neuropathic itch, is usually caused by nerve injury and can arise at any point along the afferent pathway of the neurons. This itch is observed for example after a varicella zoster infection or nerve trauma. Itch that is originated from activation of the central nervous system is called neurogenic itch. The underlying mechanism is complex since it involves pruriceptive itch as well. This itch is often observed in visceral disease states such as end state renal disease or kidney failure. The last subtype of itch is termed psychogenic itch. This type of itch arises with somatization and the delusional state of parasitophobia [66–68]. In this chapter, we will focus on pruriceptive itch and the translational model for it.

Generally, theories have been proposed that explained the relation between itch and pain. Itch is mediated through weak activation of nociceptors and stronger activation would result in weak pain. This is also called, the intensity theory. However, further research has elucidated new aspects that explain pruriceptive sensory mechanism in the nervous system. This resulted in two main pathways including specificity and pattern theories. The specificity theory, explains that there are different sets of neuron fibers transferring information to the central nervous system which send responsive signals including itch and pain [25, 35]. The pattern theory stipulates that many sensory receptors and spinal cord neurons are involved in sensation of itch [69]. Although, the neural mechanism of pruritus has been investigated extensively, there remains much to be learned. Therefore, studies that use chemical agents to induce itch have been designed to study the sensory patterns of itch and pain in humans.

One of the most frequently and widely used pruritic agent, that evokes itch, is histamine [70]. Originally, histamine is a neurotransmitter that is associated with pathological processes such as inflammation, pruritus and vascular leak. Histamine is stored in several immune cells, basophils and mast cells and is quickly released after stimulation. Stimulation with histamine, triggers the unmyelinated nerve fibers, also known as C-fibers. A subset of C-fibers (CMI or CMIh) is stimulated according the intensity of the stimulus. In case of histamine stimulation, sustained response of CMI occurs [71]. Histidine decarboxylase (HDC), an enzyme that is responsible for histamine production, increases through stimulation with certain mediators that are found in skin lesions of patients with atopic dermatitis. Hence, this enhancement is associated with upregulated histamine release and thus with increased itch sensitivity [28, 70].

Histamine has been used in literature as an important inflammatory mediator that is responsible for vascular and inflammatory effects [33]. In the early 1900s the first studies were conducted regarding the potential vascular role of histamine in vivo, however, only a couple of years ago a clinical study was conducted that investigated the cutaneous inflammatory response in human skin. Falcone et al. has developed an easy-to-use model to study the early stages of skin inflammation. Eighteen (18) subjects with Fitzpatrick skin type II and III received topically applied histamine after performing histamine iontophoresis. The subject had to
rate their perceived itch on visual analog scale (VAS) with 3 being the threshold for willingness to scratch the skin. Additionally, different skin assessments were performed including trans-epidermal water loss, skin redness and punch biopsy to process immunohistochemistry. Itch was observed up to 30 minutes after stimulation with histamine iontophoresis and was above the itch threshold (VAS > 3). Immunohistochemistry showed an increase of the epidermal thickness, after 72 hours of histamine iontophoresis challenge. In summary, this model can be used as an in vivo model to provoke local and acute skin inflammation, without having an impact on the barrier function. However, no data are available on cell level or cytokine expression profiles [29].

As was earlier described, increased production of histamine has been related to several skin diseases including atopic dermatitis. In addition, histamine has been the main prototypical pruritogen that has been used for experimental purposes. The working mechanism of histamine is going via G-protein coupled receptors: H1 up and till H4. It appears that the H1 and H4 receptors play a role in the histamine involved itch response in mice. In humans, the involvement of other receptor subtypes (H2 and H3) in itch is not well-examined in literature [31, 32]. Generally, the classical anti-histamines bind to H1 receptor and are prescribed in patients suffering from atopic dermatitis. However, recent research clarifies that histamine pathway is not playing a major role in atopic dermatitis. Also, the clinical use of anti-histamines in atopic dermatitis population has been ineffective and questionable which corroborates these findings [27 , 32, 72].

Therefore, there was a need to establish an alternative itch model, relating to another pathway. The pruritus pathway has physiological functions such as skin barrier homeostasis, inflammation, itch and pain and is the protease-activated receptor (PAR) pathway. PARs are classified as G-protein-coupled receptors and consist of four members, PAR-1, PAR-2, PAR-3 and PAR-4, whereas PAR-2 pathway is mainly associated with skin diseases such as atopic dermatitis [26]. Papoiu et al. established a simple human model based on exogenously stimulation of the PAR-2 pathway in order to provoke itch by applying Cowhage spicules. Additionally, the Cowhage model was compared to the traditional histamine iontophoresis model and the effect of the combined model (histamine iontophoresis and Cowhage) was observed. VAS rating was increased in both atopic dermatitis patients and healthy volunteers, the Cowhage and combination model compared to the histamine model, resulting in no synergy between the Cowhage and the combined model. This finding suggests that Cowhage was the major contributor of itch after stimulation of both pathways simultaneously [34]. The Cowhage model is simple and easy to use and could serve to study itch related skin diseases such as atopic dermatitis. On the other hand, less is known about this pathway and more research is required to examine the mechanism behind this model.

In conclusion, two main skin challenge models were described to provoke itch: histamine iontophoresis and Cowhage. Both models are suitable to use, however, both have a different underlying mechanism to elicit the itch sensation. Evidence-based, induction of the PAR-2 pathway plays a major role in atopic dermatitis, causing pruritus, compared to the histamine model. Therefore, from a therapeutic point of view, drugs that inhibit PAR-2 itch pathway, could be promising, leading to development of a new treatment for chronic pruritus. Since less is known about the underlying cellular mechanism of Cowhage, it would we useful to examine biomarker expression, conduct different skin photography assessments and look at the skin vascularity flow. Furthermore, an advanced challenge study is required in healthy volunteers and patients with atopic dermatitis to examine and monitor the inflammation of both models. In addition, the efficacy of anti-histamine agents and PAR-2 antagonists could be evaluated as well.
4. Model for inflammation and pain: UV-B skin irradiation

Ultraviolet (UV) radiation is classified as a carcinogenic compound since it has the ability to initiate and promote malignant skin tumors. Additionally, increased exposure to UV radiation can lead to other skin problems such as inflammation and degenerative aging. UV energy is subdivided into three main classes based on physical properties: UV-A, UV-B and UV-C. UV-B can cause physiological skin alterations leading to a cascade of cytokine activation and resulting in an inflammatory response, so called “sunburn”. Furthermore, exposure to UV-B is related to the accumulation of epidermal keratinocytes and thereby increases the epidermal thickness. UV-B radiation has an additional effect on the skin, it is able to up-regulate the production and the accumulation of melanin in the skin and is also linked to cancer susceptibility.

In well-controlled clinical settings, exposure to UV-B is widely used as a human and animal challenge model to induce local cutaneous hyperalgesia (pain) and inflammation. Primary hyperalgesia is induced after 24 hours and remains for more than 48 hours which makes the model suitable for studies where multiple dosing is required. The amount of UV-B radiation applied to the skin needs to be adjusted to a subject's skin type, according the classification of Fitzpatrick Skin Type [73, 74]. Hereafter, prior the start of the challenge, the Minimal Erythema Dose (MED) is determined and subsequently a one-, two- or threefold multiple of this dose is applied to the skin. After 24 hours, skin inflammation occurs.

This UV model is one of the pain models that can be used as a screening tool for early stage clinical drug development. However, in research, the UV model is used to examine the effects of anti-analgesic or local anesthetics [75, 76]. Recently, an article was published where the UV-B model was one of the models that was applied to compare the effects of several analgesic to placebo. The following analgesic compounds were investigated in the first part: fentanyl, phenytoin, (S)-ketamine and placebo. For the second part of the study imipramine, pregabaline, ibuprofen and placebo were examined. Different pharmacodynamic (PD) assessments were performed which are part of the pain cart including thermal grill, thermode testing and UV-B, electrical stimulation test, pressure stimulation and cold pressure test [41]. Whilst, this study was performed to examine systemic effects of analgesic compounds, the topical effect of UV-B radiation was not determined. One article published the effects of single doses of UV-A, UV-B and UV-C on skin blood flow and barrier function by laser-Doppler flowmeter and evaporimetry. Radiation with various UV light resulted in skin inflammation characterized by erythema, however, assessed visually. Visual perception of erythema correlated with the increase in blood flow assessed by laser-Doppler flowmeter. However, UV radiation has not damaged the skin barrier function, since the trans-epidermal water loss was not increased. An exception formed the three MED, an increase in blood flow was observed after 2 weeks [38]. This study has examined the effects of analgesics on UV-B radiation and other models evoking pain, while skin inflammation occurs as well. Only a few in vivo studies attempted to examine the effect of UV-B radiation on skin inflammation. In general, UV-B radiation triggers the production of inflammatory cytokines in the human keratinocyte cell line HaCaT, including IL-1, IL-6, IL-8, IL-10 and TNF-α, which are leading to alterations of immune cells of the skin [39]. However, involvement of immune cells in skin inflammation after UV-B radiation has not yet been examined and monitored in healthy volunteers.

For future perspectives, the UV-B challenge model could be applied to induce temporarily skin inflammation that could be monitored with additional dermatological tests, such as multispectral imaging, thermography and laser speckle contrast imaging.
5. KLH challenge

Challenge models that are described in this chapter, were mostly initiating an innate response, except the imiquimod challenge model. However, in auto-immune skin diseases, activation of the adaptive immune system is crucial as well as the involvement of T-cells [77]. It is quite challenging to evaluate the efficacy of novel drugs in healthy volunteers that target T-lymphocytes, since these are in the resting phase. Hence, challenge models could provide the desirable solution by activating autoreactive T-cell pathways in healthy volunteers. Earlier research investigated keyhole limpet hemocyanin (KLH) as a potential immunization candidate for studying the cell-mediated immune response [78]. KLH is a large molecule (~8000 kDa) consisting of several subtypes and has been widely used in animal and human research for more than 40 years to outline cellular and humoral responses [79–81]. Additionally, KLH can be used as a carrier protein for cancer vaccines and for bladder cancer immunotherapy [20, 82]. Because of the xenogeneic properties to the human immune system, KLH is able to promote a reliable primary immune response. The following administration routes are known and have been used in earlier research—intradermal, subcutaneous, intramuscular and inhalational [21, 22, 83–87]. Furthermore, KLH is considered to be clinically safe, since no reports are available on significant adverse events as reported in the comprehensive review by Harris & Markl. Only mild adverse events were reported including itch, rash and mild injection site reactions (soreness) [19, 88]. In summary, single dose immunization with KLH evokes a predictable primary T-cell dependent immune response. An additional intradermal dose of KLH will result in an additional immune response and thereby induces a delayed type IV hypersensitivity reaction around the site of injection [78].

Presence of erythema and induration are features of a cell-mediated immune response and are generally scored by visual inspection, which is a subjective method and may lead to significant interrater variability. Saghari et al. established a challenge model to activate T-cells in healthy volunteers after immunization with KLH, whereas both the cellular response and the delayed type hypersensitivity are objectively quantified. Adaptive immunity was measured by anti-KLH IgM and IgG blood serum level titers. Additionally, cutaneous blood perfusion, erythema and swelling were objectively measured by respectively laser speckle contrast imaging (LSCI), multispectral imaging and colorimetry. An increase in anti-KLH IgM and IgG was observed after intramuscular KLH administration compared to placebo. This was the case for the cutaneous blood perfusion quantified by LSCI and for the erythema and swelling quantified by multispectral imaging and colorimetry. So far, none of the studies have quantified induration and erythema response by using non-invasive instruments. This model is developed as proof-of-concept to determine the feasibility and to quantify the features of cell-mediated response [89]. Therefore, the delayed type hypersensitivity model can serve as a candidate to study the pharmacological and pharmacodynamic effects of immunomodulators in healthy volunteers.

6. Conclusion

Generally, in vivo mice models are a crucial part in pre-clinical drug developmental programs, assessing safety. However, often animal models lack the disease or differ in morphological and physiological properties. Ethical concerns with regard to animal studies are an additional issue which prompts to search for new solutions. Currently, safety is assessed in healthy volunteers who hamper the disease.
Therefore, challenge models that mimic the disease temporarily, could provide a possible solution and act as translational models. This chapter has provided an overview (Table 1) of various challenge models that are known to initiate skin inflammation by triggering the human immune system. First, the human imiquimod challenge model was introduced as a safe and well-tolerated model to study temporarily induced skin inflammation by targeting the TLR7/8 receptor. The effect on erythema, cutaneous perfusion and biomarker expression was more pronounced in the group with the perturbed skin barrier due tape stripping. Nowadays, this imiquimod model can be applied to test agents that target TLR7/8 receptor with anti-tumor characteristics.

Furthermore, two models for pruritus were described focusing on two different mechanisms. The first model used histamine as pruritogen to evoke itch via a subset of C-fibers. An upregulation of HDC is associated with an increase in histamine release and is found in the lesions of patients suffering from atopic dermatitis. Anti-histamines are often prescribed against itch in patients with atopic dermatitis even though they are ineffective. Therefore, an alternative model was developed targeting the PAR-2 pathway. In this model, itch was initiated by applying Cowhage spicules to the forearm of healthy volunteers and patients with atopic dermatitis. The itch sensation was based on VAS score and EASI (in patients with atopic dermatitis), both giving qualitative measures.

Another model that has been described in this chapter is the UV-B radiation model, which is used to induce pain stimulus in healthy volunteers. A couple of studies elucidates the occurrence of skin inflammation after UV-B radiation. However, no research has been done that focuses on skin inflammation in humans after using UV-B radiation.

The last model of this chapter triggering neo-antigen, is the KLH challenge model in healthy volunteers. KLH caused a delayed type IV immune response. An increase in cutaneous blood perfusion, erythema and swelling was observed after administration of KLH. This model could be used for proof-of-concept studies.

In general, all the challenge models that have been developed could be optimized by assessing pharmacodynamic endpoints focusing on the four pillars imaging, biophysical, clinical and cellular/molecular that together constitute a so-called ‘dermatological toolbox’. For imaging, various tools can be used such as multispectral imaging, 2D/3D imaging, colorimetry and optical coherence tomography. Laser speckle contrast imaging, trans-epidermal water loss, thermography, transdermal analysis patch and microbiome analyses are able to provide objective information on biophysical condition of the skin. For completeness of the derma toolbox it is recommended to include the NRS pain/itch or VAS as well as the skin histology, immunohistochemistry and mRNA expression. This toolbox will allow us to develop and monitor advanced human skin challenge models that will provide a more holistic view and to move a step closer towards ‘systems dermatology’.

Conflict of interest

No conflicts of interest.
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