

The continuing evolution of targeted therapy for inflammatory skin disease

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Abstract Treatment of inflammatory skin disease has evolved from non-specific suppression of immune cells to increasingly precise targeting and modulation of immune mechanisms at all levels. This has led to dramatic treatment successes and deepened understanding of the pathophysiology. The cycle of in vitro studies, animal models, clinical trials, and case series of non-primary indications is a feedback loop that informs and guides the design of ever better disease models and therapeutic targets. Not only are we constantly discovering new molecules driving skin inflammation, we have also found that psoriasis and other autoimmune conditions are driven by distinct mediators occurring in early and late phases, which could be an opportunity for phase-specific or multipronged interventions. The deeper our mechanistic understanding, the more likely we will be able to discover subtle strategies to reprogram each patients' immune cells without having to dampen or eliminate their protective effects against pathogens and tumors. Lastly, ongoing genomic studies might soon confirm interesting genetic markers for predictive personalized medicine, the earliest currently being evaluated in psoriasis such as *HLA-Cw6* and *TNEAIP3*. Taken together, the continued evolution of immune therapies in skin will potentially allow an unprecedented form of medicine that is not bent on silencing the pathogenic mechanism, but rather

aims at using subtle interventions to shepherd the immune cell swarm back on the correct path.

Keywords Biologics · Inflammation · Swarm · Combined · Phase-specific

Introduction

Thanks to novel insights into the genetic and immunological background of inflammatory skin disease, we have today a better understanding of the complex molecular and cellular events that initiate and maintain inflammation in cutaneous pathology. Increasingly realistic concepts of the pathogenesis have driven the development of targeted therapies with unprecedented clinical efficacy. In turn, feedback from translational and clinical studies of patients treated with targeted therapies is continuously utilized to guide the refinement and validation of these disease concepts (Fig. 1) [1].

Good examples for this mechanism are the discovery of the role of TNF- α in psoriasis by initial chance observations and subsequent clinical trials, which improved our understanding of psoriasis models enormously.

In this article, we will first discuss the growing family of targeted therapies under the viewpoint of emerging models of inflammatory skin disease, namely the dichotomous models of triggering vs. maintenance and suppression vs. deviation of immune responses, and evaluate conclusions that can be drawn from observing clinical outcomes in patients under this view. We will revisit the question whether immunopathology is formed by a single long-lasting period of immune cell activation, or a series of short-lived activation triggers, or rather a combination of both. Subsequently, the review addresses whether we should strive to silence unwanted immune cells or rather try to reprogram them. Then, we will evaluate the

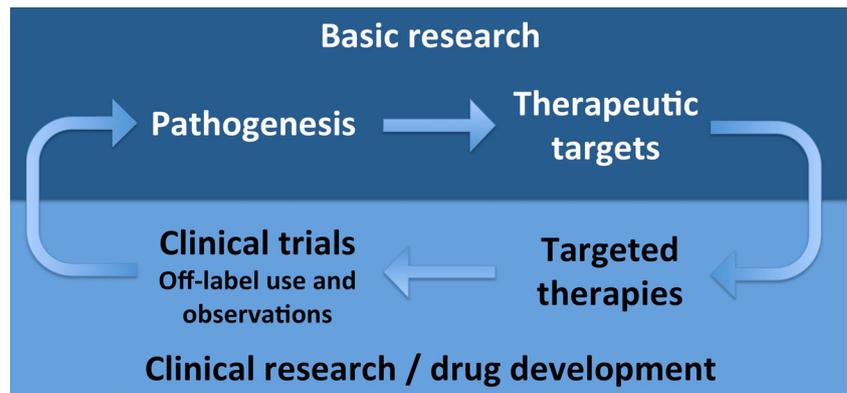
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Fig. 1 The cycle of induction and deduction: from pathogenesis to targeted therapies and back



hidden potential of synergic therapy, where two or more targets with known synergic pathogenetic effects are targeted simultaneously to achieve a greater therapeutic effect. Lastly, we will discuss what we can learn by observing clinical outcomes of our patients. The advantages and disadvantages of large-scale clinical trials are compared with careful, detailed observations of small cohorts of patients treated with targeted therapies through the eyes of physicians and scientists with a profound understanding of the underlying pathomechanism.

Targeted therapies for early and chronic cutaneous inflammation

Most inflammatory skin diseases are chronic in nature, but the clinical course can range from relatively stable diseases such as stable plaque-type psoriasis to chronic-relapsing diseases with sudden exacerbations such as pustular psoriasis or atopic dermatitis [2, 3]. Clinical observation shows that diseases segregate into acute-onset/relapsing pattern vs. long-lasting, chronic courses, such as sometimes seen in psoriasis type I and II [4]. Sometimes, it seems to us that the former type can be more easily treated, while the latter patients' lesions are difficult to influence therapeutically. The triggers that initiate those two distinct patterns may be distinct as well. Indeed, sterile inflammation in the initiation phase of inflammatory skin disease is mediated by the innate immune system and can thus be classified as autoinflammatory [5, 6]. Autoinflammation is driven by endogenous danger signals, metabolic mediators, as well as cells and cytokines of the innate immune system such as IL-1, IL-8, and TNF- α . Late inflammation, on the other hand, is considered to be driven and maintained, respectively, by activated cells of the adaptive immune cells, mainly T cells in the case of cutaneous inflammation [1]. Therefore, cutaneous inflammation in skin disease can be viewed as consisting of two phases of overarching but distinct types of inflammation: (1) an autoinflammatory phase, driven by endogenous or exogenous triggers, mediated by the innate immune system, and implicated in initiating disease and (2) an autoimmune phase, which is initiated by

these autoinflammatory events but mediated by the adaptive immune system. The autoimmune phase is considered to play the predominant role in chronic stable disease [6].

A typical example of such interplay between autoinflammatory and autoimmune inflammation in skin disease can be observed in plaque-type psoriasis (Fig. 2). According to the clever model of biphasic immune activation [6], psoriasis lesions are initiated by constantly repeated short bursts of innate inflammation, consisting of toll-like receptor activated dendritic cells, rapid release of cytokines of the IL-1 family, and recruitment of neutrophils. In a transitional period, T helper type 17 cells (Th17) are attracted and activated by dendritic cell (DC)-derived IL-23 and, likely together with neutrophils, release large amounts of IL-17 [1, 7]. Then, an immunological switch takes place with the dendritic cells starting to produce IFN- α . This cytokine antagonizes IL-1 family member cytokines, suppresses the Th17 response, and initiates a classical Th1-dominated cytokine milieu with the influx of IFN- γ -producing Th1 cells and macrophages, thus heralding the beginning of the chronic stable stage of inflammation [8]. In this process, differentiation of Th1 cells is dependent on IL-12 produced by macrophages and DCs. Taken together, in classical psoriasis plaques, bursts of innate autoinflammation coexist with T-cell-driven autoimmune inflammation [6]. The corresponding histopathological features are infiltration of activated innate immune cells such as mast cells and neutrophils in developing psoriatic lesions and a predominance of activated T cells and macrophages in stable psoriasis lesions [3, 9, 10]. The corresponding clinical features are pustular eruptions for highly acute psoriasis and pitted nails due to recurrent neutrophil eruptions in the nail bed as a sign of recurrent local autoinflammation.

A similar dichotomous or biphasic view on the inflammatory process can be applied to atopic dermatitis: [2]. In the initiation phase of allergic skin inflammation, exogenous triggers such as allergens (e.g., house dust mites), viruses, and bacteria (e.g., *Staphylococcus aureus*) induce the production of innate cytokines like thymic stromal lymphopoietin (TSLP) and IL-33 from keratinocytes [11] which in turn induce secretion of IL-5 and IL-13 from innate lymphoid cells (ILCs) and

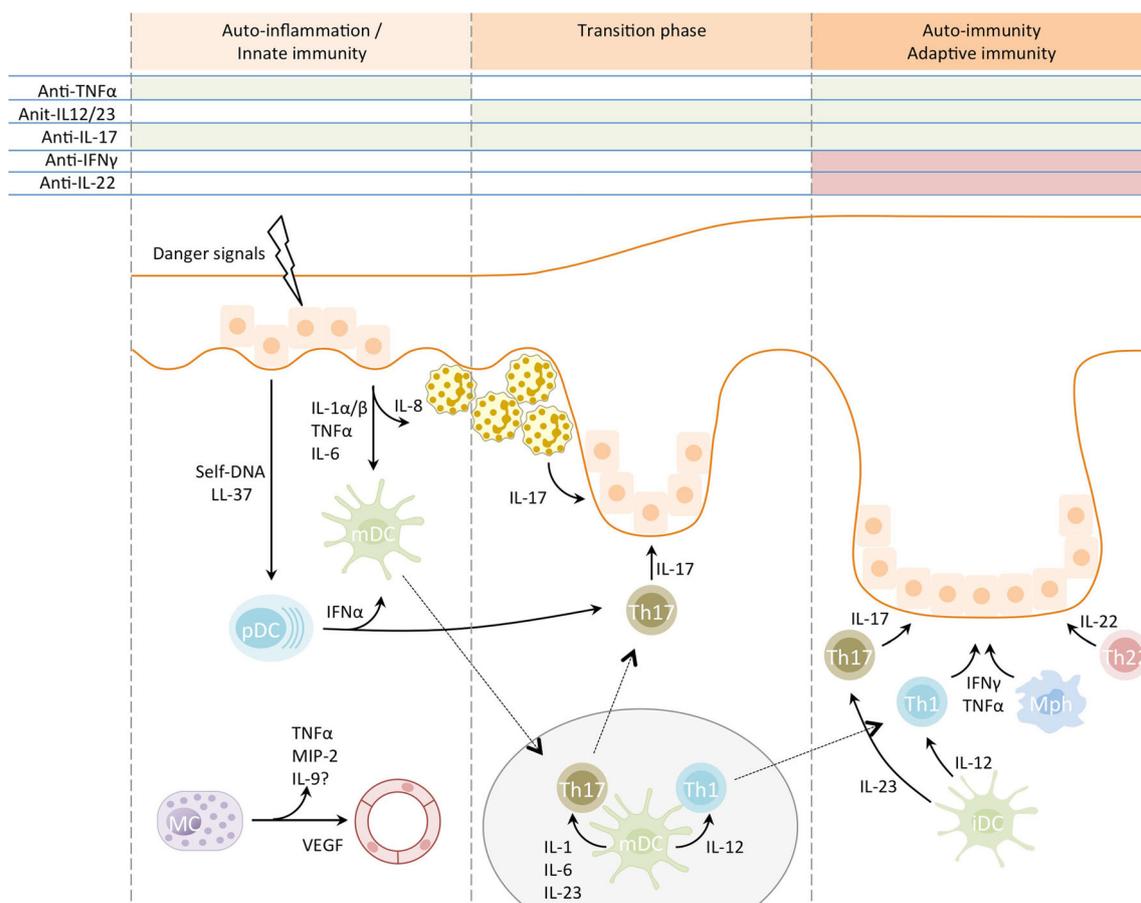


Fig. 2 Three phases of the immune mechanisms driving inflammatory disease

IL-10 from Langerhans cells [12, 13]. This initial innate immune response triggers a mixed innate/adaptive transitional phase where Th2 cells are activated to produce more IL-4, IL-13, and IL-31 [13, 14], B cells undergo isotype class switch to produce IgE antibodies, and eosinophils and basophils start to infiltrate the skin. Finally, in the chronic stage of atopic dermatitis, the inflammatory picture is dominated by adaptive immunity with Th22 cells and Th1 cells producing IL-22 and IFN- γ , respectively. The differentiation and maintenance of these T cell subsets are thought to be maintained by IL-12 secreting myeloid dendritic cells (mDCs), which are also abundantly found in the immune infiltrate of chronic AD [1].

As for psoriasis, these sequential inflammatory processes are also reflected in the histopathological and clinical presentation: histopathology of acute AD shows epidermal changes with intercellular edema (spongiosis) and activated LCs and a beginning dermal infiltrate consisting of mast cells, T cells, and monocytes/macrophages. In chronic lesions, macrophages/dendritic cells and T cells dominate the dermal infiltrate, with a few eosinophils and non-degranulated mast cells [15]. Clinically, early AD lesions are characterized by inflammatory papules and vesicles on a background of erythema, whereas

chronic lesions present with infiltrated, fibrotic plaques with scales and lichenification [16].

Taken together, both in psoriasis and AD, the immunopathologic process is characterized by distinct but partially overlapping inflammatory phases, namely an early autoinflammatory phase orchestrated by the innate immune system and a chronic autoimmune phase, dominated by cells and cytokines of the adaptive immune system.

Today, a plethora of targeted therapies to inhibit multiple of the abovementioned inflammatory pathways are either approved or currently in clinical trials. For psoriasis, the approved therapies with long successful clinical track records target TNF- α or IL-12/23p40. This group of highly effective biologics was recently joined by monoclonal antibodies targeting IL-17 or its receptor, showing impressive therapeutic efficacy. In contrast, monoclonal antibodies targeting IL-22 or IFN- γ have shown disappointing results in clinical trials in psoriasis, failing to induce major improvements in most patients [1, 17]. This divergent therapeutic efficiency of inhibiting distinct inflammatory pathways now provides the basis for validation of established pathogenesis models and reflections on the true contributions of these molecules to pathogenesis. For instance, the striking difference in the

ability to inhibit psoriatic inflammation of anti-IL-17 compared to anti-IFN- γ antibodies, despite similar expression levels in situ of these two cytokines [18], raises questions on the respective pathogenetic contribution of these two cytokines. A straightforward explanation, of course, attributes a lesser pathogenetic role to the IL-12/Th1/IFN- γ axis and a central pro-inflammatory role to the IL-23/Th17/IL-17 axis, thus elegantly explaining the diverging clinical efficiency of blocking either pathway. However, given the manifold and well-established pro-inflammatory effects of IFN- γ on immune and non-immune cells [19], many of which have been intimately linked to psoriasis pathogenesis [20, 21], the true answer might be more complicated. Similar reflections apply to the cytokine IL-22. Translational research has identified IL-22 as a key proinflammatory cytokine in psoriatic skin inflammation linking immune and epithelial cells [22], yet antagonism of this cytokine does not seem to be very efficient in improving the skin condition of psoriasis patients [1]. Again, it can be postulated that IL-22 does therefore not play a major pathogenetic role, but a more careful look at emerging models of cutaneous inflammation might provide new insights.

One viewpoint under which these observations can be dissected is the concept of early and chronic or autoinflammatory and autoimmune inflammation, as introduced above. Looking at the outstanding clinical efficacy of neutralizing TNF- α , IL-12/23p40 or IL-17 and the lack of benefit from blocking IFN- γ or IL-22, it could also be imagined that, to achieve therapeutic effect, it is necessary to inhibit inflammatory signals that act in both the early and the late phase of inflammation (Fig. 2), or to inhibit signals that play an intricate role in bridging these two phases. For example, TNF- α is expressed in the very early phases of innate inflammation by stressed keratinocytes but remains a key cytokine in the chronic phase, where it is abundantly produced by Th1 cells, macrophages, and activated keratinocytes. Thus, antagonizing TNF- α will suppress both the early innate and the late adaptive immune response, leading to downregulation of initiating as well as maintaining inflammatory signals and therefore to successful treatment of psoriasis. Similarly, DC-derived IL-12/23p40 is involved in bridging innate and adaptive inflammation, as it is expressed after DCs sense innate danger signals and then leads to activation of an adaptive Th1 and Th17 response. Therefore, by blocking IL-12/23p40, interference with both the autoimmune and the autoinflammatory phase is established and, consequently, successful treatment of psoriatic inflammation is observed clinically. These reflections may also apply to the high efficacy of neutralizing IL-17 signaling in psoriasis, as IL-17 is increasingly understood to be an intricate part of both the early innate and the late adaptive immune response [7, 23].

Under the same view, the lack of therapeutic benefit from blocking IFN- γ or IL-22 signals in psoriasis could be explained by their predominant involvement in late autoimmune but not early autoinflammatory phase of inflammation [24].

As a consequence, ongoing innate stimulation and positive feed-forward loops are not inhibited and continue to trigger adaptive inflammation. The concept that abrogation of both phases of inflammation is necessary to successfully treat psoriasis is further supported by the conspicuous absence of reports showing clinical benefit from blocking early innate mediators such as IFN- α (MEDI-545) and IL-1 (by anakinra for $\alpha\beta$, canakinumab (β), rilonacept (β) and MABp1 (α)), despite the mentioned biologics to neutralize these signals with proven clinical efficacy in inflammatory skin diseases that are characterized by dominating innate immune activation such as neutrophil dermatoses and pustular psoriasis [25–27].

The same concept can be used to analyze efficacy of targeted therapies in atopic dermatitis, although clinical experience with these drugs is considerably smaller than in psoriasis and clinical trials have just started on a broader scale recently [28]. Therefore, only data from clinical trials on neutralizing antibodies against IL-5 (mepolizumab) [29, 30] and IL-4R α (dupilumab) [31, 32] are available as well as a few reports from case series using anti-IL-6R and anti-CD20 antibodies in atopic dermatitis [33, 34]. In clinical trials, anti-IL-5 therapy did not show any therapeutic effects whereas anti-IL-4R α treatment, which interferes with both IL-4 and IL-13 signaling, induced marked and rapid improvement of atopic dermatitis. In the model of early and late inflammation, these diverging clinical effects can be explained by the different targets of the blocked cytokines. In atopic dermatitis, IL-5 exerts its effects in early inflammation, predominantly by promoting accumulation and activation of eosinophils in the skin, albeit it being expressed by cells of both the innate and adaptive immune system and it having effects on isotype class switching in B cells. Thus, neutralization of IL-5 will mainly interfere with attraction and activation of eosinophils in early innate inflammation but will fail to limit chronic adaptive immune circuits. In contrast, dupilumab blocks the shared alpha subunit of the IL-4/IL-13 receptor and thus inhibits pro-inflammatory signals in all cells that express either receptor. These include innate cells such as keratinocytes, dendritic cells, innate lymphoid cells, as well as adaptive immune cells such as T cells of different subsets and B cells. Therefore, blocking the IL-4/IL-13 receptor profoundly dampens innate as well as adaptive inflammation in atopic dermatitis and therefore, according to the model of bimodal immune activation in cutaneous inflammation, shows great therapeutic effect. This hypothesis is further supported in atopic dermatitis by the clinical benefit of interrupting IL-6R signaling, as IL-6 is known for its regulatory role in innate and adaptive immunity [34, 35]. It will be highly interesting to see the outcome of ongoing clinical trials in atopic dermatitis with targeted therapeutics against mediators of innate inflammation (IL-33, TSLP) and mixed innate/adaptive inflammation (IL-31, IL-22).

Another cytokine that merits attention along these lines is IL-9. Although discovered 20 years ago, it remains one of the more enigmatic cytokines so far and its cellular source, function, and targets remain incompletely understood [36]. However, a growing body of evidence points towards a role in early allergic but not late inflammatory processes, with remarkably transient IL-9 expression early after cellular activation [37–40]. Therefore, IL-9 might be a model cytokine with a unique role in early transient immune activation but no importance for chronic inflammation. In accordance, the only clinical trial attempting at blocking IL-9 in human chronic asthma has failed to show efficacy [41].

In summary, the clinical efficacy of blocking distinct inflammatory signals in cutaneous disease with bimodal immune activation might not solely be determined by the involved pathways, but also by their ability to interfere with both the autoinflammatory and the autoimmune phase of skin inflammation. If this is the case, antagonism of early innate cytokines such as IL-1 might be more suitable to prevent new flares of psoriasis rather than to treat established plaques [6] and inhibition of keratinocyte-derived signals like TSLP or IL-33 might be more suitable to treat subclinical inflammation rather than established atopic dermatitis. Questions like these have so far not been addressed in clinical trials and remain to be elucidated by curious clinicians with both their patient's wellbeing and pathomechanistic reflections in mind.

Immune deviation instead of immune blockade?

The simple concept of stopping inflammation by silencing immune signals or even destroying their cells of origin could in the future be replaced by more elegant approaches. If we assume that inflammatory conditions arise due to misguided, normally beneficial signals, one could attempt to steer the immune metabolism back in its normal and healthy channels.

There are a series of remarkable studies along these lines that have all been performed more than 10 years ago [42–44]. It appears that with the advent of monoclonal antibodies against cytokines, this idea has moved into the background, despite impressive clinical effects observed in these early studies. However, there are important lessons that likely can be learned from them that will also help understand and even predict clinical phenomena that arise or likely will arise in patients undergoing targeted therapy. On a very basic level, these studies have taught us that established inflammatory equilibria in skin lesions can be toppled by manipulating the pathways that stabilize them. For instance, treatment of psoriasis patients with recombinant IL-4 markedly improved psoriasis and induced pronounced skewing of intralesional cytokines towards a Th2 pattern while downregulating Th1/17 type inflammation [42]. Recently, the mechanism of this interesting phenomenon that works via IL-4 silencing IL-23 in

antigen-presenting cells was demonstrated [45]. Similar observations were made in psoriasis patients when treated with the anti-inflammatory cytokines IL-10 or IL-11 [43, 44]. Further investigation of the dynamics and half-life of these phenomena will yield interesting information about the stability of immune deviating strategies. This could answer whether we may ever be able to attempt a definite cure of psoriasis and other conditions with, i.e., prolonged cytokine treatments or novel vaccinations that ideally would produce a long-lasting effect.

Pathologic immune deviation could also explain intriguing observations regularly made during clinical treatment of inflammatory dermatoses, such as sudden resistance to biologics without anti-drug antibodies, paradoxical psoriasis to TNF- α antagonists, and many more.

Not addressed at all in clinical studies as yet was the question of spatially localized immune cell swarms [46] in the skin and the rest of the immune system. It has been known for a while that skin-resident T cells are stable and form a separate compartment from blood [47]. Intriguing studies on coexisting atopic dermatitis and psoriasis in the same patients [48] demonstrated that even within the skin, swarms of immune cells do not necessarily intermingle but can create a stable biological mosaic. These swarms may stem from pathologic immune deviation that could theoretically be addressed with clever topical treatments.

Finally, instead of a “horizontal” deviation such as from Th1/17 to Th2, one can also follow a strategy of immune activation to de-activation with IL-10 and TGF- β , or even the other way around such as is regularly done with success in oncology with CTLA4 and PD1 [49, 50] antibodies.

Multipronged intervention vs. monotherapy

The current system of medical intervention with immunomodulating agents is primarily focused on the efficacy of single agents. This is easily understood when considering the complexity of performing studies with multiple compounds. However, in reality, the immune system is more complex and in most instances more than one signal is involved in creating or sustaining pathology. Therefore, it might be beneficial and efficacious to inhibit more than one cytokine during treatment. Were such a strategy be tested, it should first be shown that the target cytokines are indeed synergistic and not vertically arranged in a single pathway. Otherwise, the inhibition of the upstream cytokine could already (theoretically) achieve the maximum efficacy on its own, eliminating the need to inhibit the downstream cytokine.

Such synergistic combinations have already been analyzed *in vitro*, namely TNF- α and IL-17 and IL-1 and IL-23 [51, 52]. The cytokine combination was able to potentiate the result of the *in vitro* readout by several hundred-fold compared

to what each single cytokine could achieve on its own—demonstrating the power of this strategy. It follows that also the success of cytokine inhibition could be improved dramatically by utilizing this effect. Very soon, such drugs will be in phase III clinical trials, including AbbVie's ABT-122 bispecific antibody against IL-17 and TNF- α , Sanofi's tetravalent bispecific tandem immunoglobulin (TBTI) against IL-4 and IL-13, and others. Such fixed combination drugs inhibiting two or more cytokines fit very well in our current system of clinical trials and registration, even though the information of contribution to the final effect may be lost.

In dermatology, we have the unique opportunity to combine systemic drugs with topical agents. This field has been little investigated, with early surprising results, including temporary loss of efficacy by combining two monotherapies [53]. So far, interesting questions such as to the effect of systemic TNF-antagonism together with local calcineurin-inhibition have not yet been addressed.

Treatments based on large randomized placebo-controlled trials vs. Sherlockian observatory approach

Clinical medicine is both blessed and burdened with large randomized controlled trials (RCTs) for virtually every important intervention. These large and hugely costly studies are currently considered a *sine qua non* for drug registration. Unfortunately, they also have many disadvantages that we cannot exhaustively enumerate here. Evidence hierarchies place RCT at the top, which however should not lead to a black-or-white worldview and discounting of all other, non-RCT evidence. We are all aware that for practical reasons only a part, possibly not even the majority of all diseases, can be studied by RCTs. Evidence on the rarer diseases or subtypes of common conditions, very young and old patients, ethnic minorities and the like tends to come from non-RCT studies including case reports. Although all such evidence needs to be interpreted cautiously, as a whole we believe it to be often very useful, at least for clinical decision-making in the same type of non-standardized situations that gave rise to the case reports. Table 1 includes a compilation of current evidence of case reports and clinical studies broken down according to dermatosis and treatment target. Outcomes of just one case or series are put in brackets. Collection of efficacy data of targeted treatments also reveals, perhaps most accurately of all approaches, the clinically relevant pathophysiology of each disease.

Case reports have the obvious disadvantage of publication bias of positive results, non-standardized treatment schemes, and missing placebo controls. To overcome these limitations, N-of-1 [54] strategies could be promoted to replace widespread off-label use in dermatology. These are proper small

trials that closely observe the effect of an intervention in a single patient and can even be performed as a randomized controlled study by giving verum and placebo sequentially. Strategies for generic ethical approval of such interventions could be generated, so that administrative constraints do not preclude clinicians from choosing this avenue of research.

Taken together, we believe that decision-making in common and well-studied situations such as moderate-to-severe plaque psoriasis should be based on RCT results and meta-analyses. In rarer, non-standard situations however, using evidence derived from lower-quality studies, especially with independently confirmed results, might be acceptable as well as this is often the only available source of information. In our specialty with more than 2000 mostly rare conditions, case reports could thus be considered worthwhile and clinically useful contributions as long as there are no RCT available.

Conclusion

The advent of targeted therapies for inflammatory skin disease has not only heralded an era where clinicians have manifold therapeutic options and patients benefit from unprecedented clinical efficacy, it has also opened new ways of investigating the pathogenesis underlying these complex skin conditions and of validating disease models that arise from basic research. Thanks to the well-defined molecular targets of these novel drugs, it is now possible to deduce pathomechanistic processes from clinical observations to an extent that has not been allowed by previous treatments with broad biological effects. In what can be called a “circle of induction and deduction,” these insights continually feedback to and guide basic research which in turn results in the identification of novel drug targets that will eventually be tested in a clinical setting (Fig. 1). As a consequence, we are today witnessing a translational revolution of model inflammatory skin diseases, most prominently of psoriasis and atopic dermatitis [1]. The future will certainly bring further innovation and, based on large trials and huge efforts from the industry, improved and precisely tailored treatments for these frequent diseases. However, targeted therapies also hold great promise for rare inflammatory skin diseases, where medical and scientific advance mainly relies on the initiative of curious clinicians and scientists. In this setting, it seems promising to harvest the scientific potential of assessing targeted therapies in small trials where translational analysis, e.g., of sequential tissue samples before and under treatment are prone to yield a wealth of novel information on both disease mechanisms and mode of action of the investigated drug. Successful examples of such translational approaches are continuously published from all fields of dermatology and are likely to further shape the way we understand our patients and their treatments in the future [55].

Table 1 Evidence for efficacy of biologic agents for inflammatory dermatoses

Disease and observed clinical response by class of therapeutic blocking agent	IL1β/IL1Ra (inflammasome)	IL-6 (Systemic inflammatory response)	TNF-α (Macrophages / Th1)	IL-23 (induction of Th17 cells)	IL-17 (Th17 effector molecule)	CD19 (B cell surface molecule)	IgE (producing B cells / plasma cells)	LFA-1 (Dendritic cell - T cell priming)	LFA-3 / CD2 (CD4 T memory cells)
Alopecia areata	ND	ND	↓ ⁵⁶	↓ ⁵⁷	ND	ND	ND	↓ ⁵⁸	↓ ⁵⁹
Atopic dermatitis	ND	(+) ³⁴	- ⁶⁰	+/- ^{61,62}	ND	+ ⁶³	+ ⁶³	- ⁶⁴	- ⁶⁵
Behçets disease	+ ⁶⁶	(+) ⁶⁷	+ ⁶⁸	(+) ⁶⁹	ND	+ ⁷⁰	ND	ND	ND
Bullous pemphigoid	ND	ND	+ ⁷¹	(+/-) ^{72,73}	ND	+ ⁷⁴	+ ⁷⁵	↓ ⁷⁶	ND
Dermatomyositis	ND	(+) ⁷⁷	+ ⁷⁸	ND	ND	- ⁷⁹	ND	(+) ⁸⁰	ND
Dissecting cellulitis of the scalp	ND	ND	+ ⁸¹	ND	ND	ND	ND	ND	ND
Granuloma annulare	ND	(+)	+ ^{82,83}	ND	ND	(+) ⁸⁴	ND	+ ⁸⁵	ND
GvHD	ND	(+) ^{86,87}	- ⁸⁸	(+)	ND	+	ND	ND	+ ⁸⁹
Hailey-Hailey	ND	ND	ND	ND	ND	ND	ND	ND	+ ⁹⁰
Hidradenitis suppurativa	+ ⁹¹	ND	+ ⁹²	+/- ⁹²	ND	ND	ND	+ ⁹³	ND
Lichen ruber planus	(+) ⁹⁴	ND	↓ ⁹⁵	ND	ND	+ ⁹⁶	↓ ⁹⁷	+ ⁹⁸	+
Lupus erythematoses	+ ⁹⁹	(+) ¹⁰⁰	↓ ¹⁰¹	+ ¹⁰²	ND	+ ¹⁰²	ND	+ ¹⁰³	(-) ¹⁰⁴
Necrobiosis lipoidica	ND	ND	+ ¹⁰⁵	ND	ND	ND	ND	ND	ND
Pemphigus vulgaris	ND	(+) ¹⁰⁶	+/- ^{107,108}	(-) ¹⁰⁷	ND	+ ¹⁰⁹	ND	↓ ¹¹⁰	ND
Pityriasis rubra pilaris	ND	ND	+ ¹¹¹	+ ¹¹²	ND	ND	ND	!/+ ^{113,114}	ND
Progressive systemic sclerosis	ND	+/- ^{115,116}	+ ¹¹⁷	ND	ND	+ ¹¹⁸	ND	ND	- ¹¹⁹
Plaque psoriasis	!/- ¹²⁰	↓ ¹²¹	+ ¹²²	+ ¹²³	+ ¹²⁴	↓ ¹²⁵	ND	+ ¹²⁶	+ ¹²⁷
Pyoderma gangrenosum	+ ^{128,129}	ND	+ ¹³⁰	+/- ^{131,132}	ND	↓ ¹³³	ND	ND	+ ¹³⁴
Sarcoidosis	ND	(!) ¹³⁵	+ ^{136,137}	- ¹³⁸	ND	- ¹³⁹	+	ND	+ ¹⁴⁰
Sjögren's syndrome	ND	- ¹⁴¹	(-) ¹⁴²	ND	ND	+	ND	ND	ND
Subcorneal pustulosis Sneddon-W.	ND	ND	!/+ ^{143,144}	ND	ND	ND	ND	ND	ND
Sweet's syndrome	+ ¹⁴⁵	ND	+ ¹⁴⁶	ND	ND	ND	ND	ND	ND
Toxic epidermal necrolysis	ND	ND	+ ¹⁴⁷	ND	ND	(!) ¹⁴⁸	ND	ND	ND
Wegener's disease	ND	ND	- ¹⁴⁹	ND	ND	+ ¹⁵⁰	ND	ND	ND

! blocking drug can elicit disease, () one case or series only, ND no data

As the field of translational medicine continues to evolve and the number of available targeted therapies increases, we will undoubtedly see further refinements of current disease models. The concept of bimodal immune activation postulating that early inflammatory events are distinct from, but intimately linked to, later chronic inflammation has the potential to introduce different treatment modalities for patients with acute or

chronic disease and to prompt the development of relapse-preventing therapeutics [6]. Animal models used in basic research can be validated by careful comparison with clinical studies of targeted therapies, thus assessing strengths and weaknesses of the respective models. Combined inhibition of targets with synergistic pathogenic potential will likely add highly effective treatment options for patients with recalcitrant disease.

In summary, targeted therapies have profoundly influenced not only the treatment but also the understanding of psoriasis and are likely to have a similar impact on other model inflammatory skin diseases such as atopic dermatitis. Further translational research in this field holds the promise that similar developments will also take place in less common inflammatory skin diseases, making the impressive therapeutic potential of targeted drugs available to many more patients while teaching their doctors valuable lessons about the underlying disease.

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