Dermatology Practical & Conceptual

Novel Vehicles For Drug Delivery in Atopic Dermatitis: A Narrative Review

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ABSTRACT

Introduction: Atopic dermatitis (AD) causes dry and itchy skin and inflammation that severely impairs the quality of life of affected children and adults. While topical glucocorticosteroid application is typically the first-line treatment of choice, steroid treatment is associated with side effects and, increasingly, patient concerns about prolonged use. Novel drugs and drug delivery vehicles are required for patients with AD.

Objectives: To summarize the current literature on novel topical agents for atopic dermatitis and novel delivery vehicles.

Methods: A literature search was conducted, and a narrative review was compiled to summarize recent evidence.

Results: Novel topical drugs approved or in late-phase clinical trials for the treatment of AD include the Janus kinase inhibitor ruxolitinib, the phosphodiesterase-4 inhibitors crisaborole, and roflumilast, and the aryl hydrocarbon receptor activator tapinarof. While current topical drugs for AD are delivered via creams, ointments, gels, and related vehicles, novel delivery approaches such as electrospun patches, sprays, liposomes, nanoparticles, and lasers are being developed to enhance transdermal delivery, reduce side effects, and increase treatment adherence.

Conclusions: Topical application of creams or ointments is currently the predominant vehicle for the delivery of atopic dermatitis drugs. In vitro studies on novel vehicles show promising results to overcome the issues associated with topical delivery. Still, these findings have to be corroborated by controlled studies with human patients in the future.

Introduction

Atopic dermatitis (AD) is a chronic cutaneous disorder that affects up to 30% of children and 20% of adults depending on the geographical region [1,2]. This chronic type of eczema is characterized by dry skin, pruritus, eczematous lesions, and lichenification [3,4]. The multifactorial etiology of AD entails genetic predisposition, environmental factors, and hypersensitivity against certain environmental allergens [5]. The skin barrier is characterized by increased permeability, with disturbances in ceramide metabolism and composition fairly common in AD. This increased permeability of the skin allows for the entry of irritants, allergens, and pathogens, leading to inflammation [6].

The clinical diagnosis follows the evaluation of essential AD features (pruritus, eczematous morphology, chronicity), crucial features (early age of onset, xerosis, atopy), and several associated features [4]. Treatment options are individually chosen and encompass topical therapies, phototherapy, systemic agents, or a combination thereof [4,7]. Each of these therapeutic approaches has risks, benefits, and limitations.

For topical preparations, the vehicle by which a drug is administered maintains a central role in the treatment outcome because efficient and selective delivery of the pharmacologically active ingredient to the target site determines its efficacy. Simultaneously, the tolerability of a product and its cosmetic acceptability play outsized roles as it is incumbent upon the patient to apply the treatment for it to work regularly.

The most common vehicles for AD topical therapies are creams or ointments. Nonetheless, topical and systemic side effects are of concern with these vehicles, and their clinical efficacy varies due to the complete application on the skin [4,8]. Therefore, long-term use of topical agents, particularly steroidal drugs, is not recommended, and novel or improved vehicles are developed to increase the transport of the active ingredient to a specific target site and the drug efficacy [4].

Objectives

In the present review, the current literature on novel drugs against atopic dermatitis and their vehicles is synthesized to overview available evidence and identify research gaps.

Methods

A literature search was conducted of the various articles detailing presently used atopic dermatitis drugs and vehicles, and a narrative review was compiled to summarize recent evidence.

Results

Novel Drugs Against AD

Corticosteroids

Atopic dermatitis patients have been conventionally treated with topical corticosteroids as a first-line intervention [9]. The corticosteroids prevent antigen processing and proinflammatory cytokine release, thereby modulating the immune response [4]. Despite the efficacy of steroidal agents in reducing pruritus and eczematous lesions, their safety has been questioned, mainly when administered to sensitive body areas such as the face or used for extended periods [10]. Along with these concerns, patients' adherence to the treatment regimen may be suboptimal, resulting in aggravation and extension of the symptoms [11]. In severe atopic cases, systemic corticosteroids may be prescribed, yet due to side effects and rebound flares with such a treatment, their use is not recommended [12,13].

Ruxolitinib

Ruxolitinib is an inhibitor of Janus kinases (JAK) 1 and 2, which are involved in signaling pathways that mediate the elevation of proinflammatory cytokines [14]. Oral JAK inhibitors have been employed in treating atopic dermatitis patients. Yet safety concerns have been raised with this mode of administration due to non-specific delivery of the active drug and the development of cytopenias [15]. Theoretically, a topical agent targeted to specific affected areas could result in far less systemic exposure and, thus, a safer profile. In a phase II trial on patients with atopic dermatitis, topical administration of ruxolitinib (1.5%) twice a day significantly decreased dermatitis-associated pruritus compared to the empty vehicle control after three days of use [16,17]. This, in turn, resulted in significant improvements in patients life quality within two weeks after the initiation of therapy. Two ruxolitinib phase III trials corroborated these findings,

where topical ruxolitinib treatment (0.75% or 1.5%) was associated with a significantly more frequent success than the vehicle control treatment, and less than 1% of patients experienced side effects [18]. In a maximum-use trial of ruxolitinib (1.5% cream, twice daily for 28 days and as required during the 28 days thereafter), almost a third of the patients experienced treatment-related adverse events [19]. Long-term studies on the efficacy and safety of ruxolitinib for atopic dermatitis treatment are missing to date.

Crisaborole

Crisaborole is a benzoxaborole inhibitor of phosphodiesterase-4 (PDE-4), an enzyme responsible for degrading the second messenger cAMP in immune cells [20]. If PDE-4 is inhibited, cAMP levels rise, and inflammatory responses are modulated [21]. In two phase III trials, the condition of atopic dermatitis patients, measured as the Investigator Static Global Assessment score, improved significantly earlier and to a greater extent than in the vehicle controls at the study endpoint of 28 days [22]. The frequency of adverse events and participant retention was low, indicating good tolerability of crisaborole ointment [22]. Information on the benefits of crisaborole treatment for infants and toddlers is yet lacking, albeit atopic dermatitis frequently develops soon after birth. Hence, future investigations with this patient group are relevant.

Roflumilast

Roflumilast is another PDE-4 inhibitor with anti-inflammatory properties [23]. While this drug has demonstrated efficacy in treating chronic obstructive pulmonary disease (COPD) and asthma [24,25], clinical trials on its effectiveness in treating atopic dermatitis are ongoing. The INTEGUMENT-I phase III trial (ClinicalTrials.gov identifier NCT04773587) tested the safety and efficacy of a 0.15% Roflumilast cream, administered for four weeks, compared to vehicle control. The trial has been completed, but the results are yet to be published [26].

Tapinarof (VTAMA)

Tapinarof activates the aryl hydrocarbon receptor (AhR). AhR is a transcription factor for pro-inflammatory cytokines, which are downregulated upon AhR activation [27]. Tapinarof, therefore, acts as an immune-modulator, anti-oxidative, and anti-inflammatory treatment. In a recent phase IIb trial, topical administration of Tapinarof cream (0.5% or 1%) for 12 weeks resulted in a greater improvement of eczema and a reduced affected body area than in the vehicle control group [28]. In dose-finding studies and phase II trials, adverse events were rare and of low or moderate intensity [28,29].

Novel Vehicles for Delivery of AD Drugs

Topical Delivery

The traditional administration of atopic dermatitis treatments is the application of a cream or ointment directly on the affected skin area. Current guidelines recommend the topical administration of glucocorticosteroid class II creams for mild or transient eczema and class III creams for moderate or recurrent eczema [30]. Nonetheless, such topical administration may not ensure complete absorption of the pharmaceutically active ingredient and diminish the pharmacokinetic capacity of the drug. Moreover, long-term administration of steroidal creams is not recommended due to side effects associated with chronic exposure to the compound, including skin atrophy, telangiectasia, and striae distensae [30]. Some novel atopic dermatitis drugs, eg crisaborole, are again delivered by topical application [22,31+. With currently limited evidence for their efficacy in comparison with established glucocorticoids and calcineurin inhibitors such as tacrolimus, they are, at present, particularly recommended for those patients for whom steroid treatment is contraindicated or for those who are recalcitrant and hence cannot be treated with calcineurin inhibitors [32]. In a recent study by Thom et al, the efficacy of crisaborole ointment was compared to that of the calcineurin inhibitors tacrolimus and pimecrolimus based on patient data from randomized controlled trials that tested either crisaborole or the calcineurin inhibitors [33]. Based on this indirect comparison, crisaborole was superior to both calcineurin inhibitors in improving the Investigator Static Global Assessment scores [33]. In this context, prospective trials directly comparing both agents within the same study setting are required to judge the superiority of crisaborole over established calcineurin agents conclusively. One such trial with a comparatively small study cohort (N = 235 in four patient groups) was conducted but terminated early due to a business decision, yet initial results were obtained (ClinicalTrials.gov Identifier NCT03539601). Within the four study groups (vehicle control, crisaborole, hydrocortisone butyrate, pimecrolimus), the largest improvement was seen for patients treated with hydrocortisone, yet the organizers acknowledged that the subgroups were too small to conduct reliable statistical analysis [34]. It is also yet unclear to what extent crisaborole creams or ointments can overcome the side effects raised with glucocorticoid treatment, and their suitability for long-term treatment must be validated.

Patches are an alternative vehicle for the topical application of an atopic dermatitis drug [35-37]. These have been developed for the administration of urea and pioglitazone [35,36]. The urea patch is produced as a combination of electrospinning of poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate) fibers to generate a membrane and electrospraying

of the fibers with urea to soak the fibers in the active substance [35]. The idea behind such a patch is to enable the controlled release of the active substance, in this case, urea, and enhance its transdermal delivery. At present, there is no study assessing the efficacy of such urea patches in human subjects. Obaidat et al report the generation of polyvinylpyrrolidone fiber patches by electrospinning for the transdermal delivery of pioglitazone [36]. The results of in vitro experiments demonstrated delivery and retention of the drug in the skin [36]. Investigations on the efficacy and safety of such patches in human patients are yet to be conducted.

Another topical treatment was developed to apply botanicals in adults suffering from atopic dermatitis [37-39]. Compared to the vehicle, the botanical product yielded superior results in improving the Investigator Global Assessment scores and the affected body area [38,39]. Unfortunately, no details on the product particular characteristics or its performance in direct comparison with a competitor product were provided.

Hogue et al. tested whether applying corticosteroids in a spray rather than a cream could overcome the adherence issues observed with conventional corticosteroid treatments [40]. Patients with a history of failed corticosteroid therapy were recruited and asked to apply desoximetasone in spray form. A subgroup of the patients was reminded by phone calls to use the spray daily. The results revealed an effect of the spray vehicle and the phone call reminders on treatment adherence [40]. These findings point towards spray preparations as alternative vehicles for those patients who consider the messiness of ointment or cream vehicles as an obstacle for their regular application [41].

Nanoliposomes are developed that enclose the active ingredient within a lipid layer and thereby prevent its premature solution to improve transdermal delivery of the drug to its target site. Naeimifar et al developed a ruxolitinib emulgel with nanoliposomes and tested its efficacy on patients with mild atopic dermatitis [42]. In addition to improving dermatitis-associated symptoms such as itching and the local Scoring Atopic Dermatitis score, the skin condition at the application site was evaluated. Symptoms significantly improved after a four-week use of the nanoliposomal emulgel, and so did the skin's condition regarding hydration, melanin content, and erythema [42].

Systemic Delivery

Systemic treatment is currently only recommended for those with severe scored or persistent eczema [30]. Recommended oral systemic drugs for such cases are glucocorticoids, dupilumab, methotrexate, azathioprine, and mycophenolate mofetil [30]. The incentive for developing systemic vehicles rather than topical vehicles is to enhance the active ingredient efficacy and ensure its delivery to the target site. They typically target the entire immune system and the release of pro-inflammatory cytokines rather than the isolated inflamed skin area. Importantly, due to the risk of side effects of systemic drugs, the dose should be relatively low and be oriented on the effective topical concentration [43]. Purohit et al report on their analysis to determine the systemic tofacitinib concentration based on the concentration of tofacitinib ointment and systemic exposure after crisaborole ointment application [43,44]. Their findings indicate a proportional systemic exposure of both drugs according to the body surface area treated.

Nanoparticles

Loading an active pharmacological substance onto nanoparticles has proven efficient for delivering numerous drugs across distinct indications. For the treatment of atopic dermatitis, such nanoparticles are being developed to enhance the efficient delivery of the active substance to the target site [45,46]. These have shown efficacy in vitro for the delivery of conventional atopic dermatitis drugs such as betamethasone, hydrocortisone, dexamethasone, and tacrolimus [47-53]. No studies have yet investigated the use of nanoparticles for the delivery of novel atopic dermatitis drugs. Of note, the use of nanoparticles for the delivery of atopic dermatitis drugs must consider the potential for induction of anti-inflammatory reactions [54]. Choi et al demonstrated that the material and protein corona around the nanoparticles determines their inflammatory potential, which is relevant for inflammatory skin conditions [54]. Colloidal silica nanoparticles were found to be superior to mesoporous silica nanoparticles in terms of the inflammatory reactions in the skin following treatment and the induction of pro-inflammatory cytokines and dermatitis-associated immunoglobulins [54].

Iontophoresis

Iontophoresis entails the application of a low-voltage current to the skin to stimulate the transdermal delivery of a pharmacological agent [55]. This method has proven efficient for the administering corticosteroids for various indications, including skin diseases [56]. There are currently no controlled clinical studies with human patients that assessed the suitability of this method for atopic dermatitis drugs. In vitro data using human skin preparations revealed transdermal delivery of hydrocortisone, albeit similar efficacy was obtained by passive diffusion when healthy skin was tested [57]. However, iontophoresis resulted in significantly higher absorbance of hydrocortisone than passive diffusion when eczematous skin and psoriatic skin were tested [58]. The clinical use of this method has yet to be established for atopic dermatitis patients. A summary of the

Table 1. Novel drugs against atopic dermatitis and their vehicles for delivery.

Drug	Target/proposed effect	Available vehicles	References #
Glucocorticoids	Prevention of antigen processing and proinflammatory cytokine release	Topical/cream or spray systemic/oral nanoparticles, iontophoresis	4, 30, 40, 47-51, 57
Crisaborole	Phosphodiesterase-4 inhibitor	Topical/cream or ointment	20, 34, 58-67
Ruxolitinib	Janus kinases 1 and 2	Topical/cream or nanoliposomes	42
Tapinarof	Activation of hydrocarbon receptor and down-regulation of pro-inflammatory cytokines	Topical/cream	28, 29, 68, 69
Roflumilast	Phosphodiesterase-4 inhibitor	Topical/cream	23
Botanicals	Unknown	Topical/cream	38, 39
Pioglitazone	Reduction of pro-inflammatory cytokines	Topical/patch	36
Urea	Emollient, keratolytic	Topical/patch	35

novel drugs against atopic dermatitis and their vehicles for delivery can be found below in Table 1.

Conclusions

Current recommendations for treating atopic dermatitis currently focus on topical or systemic administration of glucocorticoids. In light of their known side effects, their limit to short-term application, intolerant patients, and diminished patient adherence, novel drugs are being developed that may overcome the limitations of steroidal medications. In addition, novel vehicles may increase the transdermal delivery of an atopic dermatitis drug and overcome side effects associated with conventional topical administration. These novel vehicles are currently under development, and their suitability for a broad clinical application is yet to be tested in controlled clinical trials. Of note, modern drug delivery vehicles such as nanoparticles are being tested based on the delivery of conventional drugs such as glucocorticosteroids, for which more pharmacokinetic data is available than for novel drugs with different molecular targets and biochemical approaches. Therefore, most in vitro studies on such novel vehicles test the transdermal crossing and the accumulation of steroids in the epidermis. Likewise, efficacy and safety data on novel drugs such as crisaborole and ruxolitinib are just emerging from phase II and III clinical trials, and conventional, topical delivery is chosen for these drugs as it is known to result in improvement of atopic dermatitis-associated symptoms in topical steroid application. Hence, the development of novel atopic dermatitis drugs and novel delivery vehicles currently happens in parallel. In contrast, novel drugs have not been tested to establish novel vehicles. Therefore, future studies must elucidate whether the highest efficacy and safety of atopic dermatitis drugs may be achieved by combining drugs against novel treatment targets with vehicles that allow a more reliable delivery of the active drug ingredient to the target site.

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