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Critical review

Therapeutics

Acne, anti-acne therapies and epidermal barrier functions: the role of adjuvant treatments

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Abstract

Introduction

Acne is the most common skin disease affecting up to 80% of both male and female adolescents. There are several different medications for the treatment of acne, both topical and systemic. Despite the fact that several drugs could be used for acne treatment, acne lesions complete cure is often very difficult to achieve. One important problem which could be considered as a major or relevant cause for this limited therapeutic success is a low patient adherence to specific acne treatments and/or recommendations from the dermatologist. The aim of this critical review was to discuss the role of treatments of acne.

Discussion

Acne treatment and in particular oral retinoids can alter skin barrier function in treated patients. Several therapies used to treat acne can induce epidermis changes altering the normal physiological skin barrier function. These alterations are responsible mechanisms for causing side effects manifesting in the skin of acne treated patients. Even if these alterations could be transient they could be a frequent reason for interrupting or stopping the treatment by the patient. An effective strategy for acne treatment should be based on a simple and effective therapy scheme taking into account that a holistic approach with adjuvant products with the aim to preserve skin barrier function and reducing skin side effects of specific treatments, could help in improving patient adherence to treatments with a consequent better clinical outcome in terms of acne lesions resolution.

Conclusion

Barrier repair therapy (the use of specific emollient/moisturising products) could represent a relevant strategy as a holistic approach of acne patients, preventing skin barrier alteration, reducing the frequency and intensity of anti-acne-specific treatments cutaneous side effects, improving patient adherence to drug treatment as a consequence of better clinical outcome in terms of acne lesion improvement.

Introduction

Acne is the most common skin disease affecting up to 80% of both male and female adolescents[1]. This skin condition occurs at all ages, from infants to adults, but primarily affects adolescents and young adults. In the population, it has been reported that people aged 15–24 years have a prevalence of approximately 85%[2]. Furthermore, there is an increase in the percentage of adult subjects in which acne remains as a chronic condition. In subjects aged between 35 and 44 years, presence of acne is reported in 3%[3]. Women are more likely to have persistent acne after 35 years of age. Acne is a condition which could have relevant negative impact on quality of life of the affected patients[4]. There are several different medications for the treatment of acne, both topical and systemic[5]. Despite the fact that several drugs could be used for acne treatment, complete cure of acne lesions is often very difficult to achieve[6]. One important problem which could be considered as a major or relevant cause for this limited therapeutic success is a low patient adherence to specific acne treatments and/or recommendations from the dermatologist[7]. Dreno et al.[8] have shown that low adherence to acne treatments could be observed in up to 50% of acne patients. Reasons associated to low adherence are: prescription of more than one anti-acne product, specific treatment-induced side effects and a poor clinical response. On the contrary, in monotherapy there are visible clinical improvements and the concomitant use of adjuvant therapies, such as specific emollient and moisturising products, are factors associated with good adherence and higher clinical success rate. These data suggest that an effective strategy for acne treatment should be based on a simple and effective therapy scheme taking in account that a holistic approach with adjuvant products with the aim to preserve skin barrier (SB) function and reducing skin side effects of specific treatments, could help in improving patient adherence to treatments with a consequent better clinical outcome in terms of acne lesions resolution. This paper discusses the role of treatment therapies for acne.

Discussion

Skin barrier alteration during systemic and topical acne treatments

A normal SB is a primary function of the epidermis[9]. SB regulates epidermal water content and the

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amount of water loss[10]. In addition, SB is important in neutralising the exogenous oxidant damage trough an innate skin anti-oxidant system[11]. An efficient SB is also important in preventing or limiting skin infections with the actions of antimicrobial peptides[12]. Skin defensive functions include the permeability barrier, retarding transcutaneous evaporative water loss and allowing survival in a very dry external environment, and an antimicrobial barrier, while simultaneously encouraging colonisation by non-pathogenic 'normal' flora, which resists growth of microbial pathogens[13]. Several skin diseases are characterised by a varying degree of SB dysfunctions[14]. Conditions such as atopic eczema, ichthyosis and psoriasis have specific and identified mechanisms which can cause SB alterations[15]. In some circumstances SB alteration could be acquired. Acne treatment and in particular oral retinoids can alter SB function in treated patients[16]. Many patients are reluctant to start treatment with retinoids because of skin irritation that is often encountered during the early weeks of their application. It is well known that oral isotretinoin causes, in almost all treated patients, relevant dose-dependent skin side effects. Isotretinoin induced cutaneous alterations are very common and are characterised mainly by xerotic and desquamative changes[17]. These alterations appear to be related to epidermal dyscohesion, and to some extent the well-known sebo-suppressive effects of the drug[18]. Skin dryness and epidermal desquamative changes induced by isotretinoin treatment commonly involve facial and acral sites. After isotretinoin oral treatment, abnormal changes in skin microflora are observed predisposing to colonisation of skin with *Staphylococcus. aureus*[19]. Alterations have also been observed in mucosal sites such as the eye, nose and lips. A severe and often troublesome side effect of oral isotretinoin is in fact cheilitis with painful lesions of the lips[20]. Moreover, increased susceptibility to staphylococcal colonisation has also been observed, probably as a result of profound SB alteration. Topical retinoids and benzoyl peroxide treatments are also associated with xerosis and skin irritation[21]. Benzoyl peroxide causes cutaneous irritation in a relevant percentage of treated patients. This agent induces damage to the stratum corneum lipid bilayer. This effect is associated with an increase in the trans epidermal water loss (TEWL) and an impairment of epidermal antioxidant potential. BP reduces vitamin E levels in the skin and it has been demonstrated that BP application causes sebum lipid peroxidation[22]. Topical retinoid treatment induces visible dermatitis changes such as erythema, scaling and desquamation in many acne patients[23]. These changes are commonly named 'retinoid dermatitis'. Topical retinoids cause enhancement of desquamation. This leads to a reduction in SC thickness with a subsequent alteration in permeability barrier functions of the skin. Therefore several therapies used to treat acne can induce epidermis changes altering normal physiological SB function. These alterations are responsible mechanisms causing side effects manifesting on the skin of acne treated patients. Even if these alterations could be transient they could be a frequent reason for interrupting or stopping the treatment by the patient.

Skin barrier function in acne patients

More recently acne researches have pointed out that skin alteration in barrier functions could be not only a consequence of specific acne treatments but also could be viewed as an inherent condition of the acneic skin. Therefore acne vulgaris could be considered as a dermatology disease characterised by a SB defect even in the absence of specific treatments able to impair SB properties. This statement is supported so far by a relevant body of evidences. In 1995, Yamamoto et al.[24] have shown that non-lesional skin of acne patients presented an increased TEWL demonstrating for the first time that SB function is altered in this condition. Modification in composition and amount of sebum were considered by this group as the culprit mechanism of SB dysfunction. Stratum corneum lipid content and composition in untreated acne patients differ from normal subjects[25]. In addition, impairment of SB functions correlate with the severity of acne. Alteration of SB functions can also be a consequence of inflammation processes characterising acne lesions formations. It has been extensively demonstrated that pro-inflammatory mechanisms are in place at the beginning of comedogenesis, therefore in the early phases of acne pathogenesis[26]. Both keratinocytes and sebocytes in the early acne formation stages express membrane receptors which could start the comedogenetic process but also an inflammation cascade. Selway et al.[27] found that toll-like receptors 2 (TLR-2) are highly expressed in basal and infundibular keratinocytes and the sebaceous gland. This overexpression of TLR-2 increases the *interleukin-1 alpha* (IL-1α) production and release, and this could be the initiating step in comedogenesis. The induction of keratinocytes TLR-2 expression seems to be induced by *Propionibacterium acnes*. Both lesional and non-lesional acne skin presents increased level of IL-1α and also aberrant integrin expression as demonstrated by Jeremy et al. in 2003[28]. Their data provide additional evidence regarding involvement of inflammatory responses in the very early stages of the acne lesion development process. In the microcomedone formation, an intense peri-follicular inflammation T-cell infiltrate has also been found in normal-appearing skin.

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This amount of experimental and clinical data pointed out that epidermal barrier dysfunction could be a central aspect in the acne pathogenesis. A proper skin care management including gentle cleansing, barrier repair and SB function maintenance is considered a crucial aspect in global treatment strategy of acne patients.

A new concept in acne therapy: the barrier repair therapy

A new and intriguing concept regarding a holistic approach to acne treatment has been underlined quite recently by Del Rosso[29]. Starting from the evidence that acne itself and therapies used may compromise the structure and the function of the epidermal barrier in multiple ways, Del Rosso underlines the importance to actively manage these changes which could deeply affect epidermal barrier function and integrity. This goal could be achieved mainly by integrating specific acne treatments to a topical barrier repair therapy (BRT) strategy. Several clinical studies have demonstrated that BRT is able to inhibit TEWL and reduce the visible skin changes observed during topical and systemic acne therapies. Effective BRT may also reduce bacterial colonisation of *S. aureus*. In addition, in acne patients under topical treatments or oral isotretinoin BRT should be used from the beginning rather than waiting until clinical visible skin changes have appeared. An 'ideal' BRT should have the capability to reduce TEWL and to recover the lipid content of the skin. Other specific ingredients can contribute to reinforce the SB. Some components of emollient and moisturising products could have anti-inflammatory ancillary action. Draelos and Ertel[30] have shown, in a randomised intra-patient trial, that the use of emollient cream containing niacinamide, panthenol and tocopheryl acetate applied 8 weeks before starting isotretinoin oral treatment was able to improve SB functions evaluated through TEWL measurements. This product was also able to induce a significant improvement in skin hydration. From a clinical point of view, these effects were associated with a better tolerability during isotretinoin treatment. Effective BRT improving SB functions trough a down-regulation of inflammatory mechanisms may also indirectly improve the antimicrobial barrier. Polysaccharides containing rhamnosoft, for example, are able to bind to keratinocytes receptors, interfering with bacterial adhesion to skin cells[31]. In vitro experiments have shown that rhamnose-based polysaccharides (biosaccharide gum-2) in a dose-dependent manner are able to reduce significantly the production of IL-1α and the synthesis of pro-inflammatory PGE2[32]. Herane et al.[33] have conducted a randomised double blind trial in 66 patients with severe acne treated with oral isotretinoin comparing the SB repair action of a specific gel-cream containing hyaluronic acid, biosaccharide gum-2 and glycerine in comparison with a placebo cream. The active product showed a significant increase of hydration of the skin reducing in a significant manner the proportion of patients presenting xerosis after 3 months of isotretinoin oral therapy in comparison with placebo (40.6% vs. 64.5%; $P < 0.05$). In addition, the group treated with the active cream did not show the increases of TEWL which on the contrary was observed in the placebo group during oral isotretinoin treatment. The conclusions of this trial were therefore that this gel-cream containing hyaluronic acid and biosaccharide gum-2 improved hydration, prevented TEWL increases in isotretinoin-treated patients, reducing the comparison of skin xerosis. These data were confirmed by Pegragosa et al.[34] who evaluated in 28 patients with severe acne and the preventing effects of this gel-cream of the isotretinoin-induced side effects. The use of this emollient and moisturising topical product reduced the appearance of skin irritation, erythema, desquamation and xerosis. This data support therefore the concept that this active gel cream was able to prevent the isotretinoin-induced SB function alteration.

Conclusion

BRT could represent a relevant strategy as a holistic approach of acne patients, preventing SB alteration, reducing the frequency and intensity of anti-acne-specific treatment cutaneous side effects, improving patient adherence to drug treatment as a consequence to better clinical outcome in terms of acne lesion improvement.

Abbreviations list

BRT, barrier repair therapy; IL-1α, *interleukin-1 alpha*; SB, skin barrier; TLR-2, toll-like receptors 2; TEWL, trans epidermal water loss.

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