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Recent advances in the understanding and management of rosacea

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Abstract

Rosacea is a chronic relapsing inflammatory facial dermatosis. There are several known triggers but the pathogenesis remains unknown. Recent achievements in understanding this disease point to the importance of skin-environmental interactions. This includes physical and chemical factors, but also microbial factors. The impairment of the skin barrier function and the activation of the innate immune defences are major and connected pathways contributing to an ongoing inflammatory response in the affected skin. This becomes modulated by endogenous factors like neurovascular, drugs, and psychological factors. These factors offer new therapeutic targets for rosacea treatment. There is a broader range of anti-inflammatory compounds available with a favourable safety record. Only recently have persistent erythema and flushing been addressed by new drug formulations.

Introduction

Rosacea is a common inflammatory facial dermatosis. It affects mainly adults, but rare cases during childhood and adolescence have been observed. The prevalence of rosacea is highest among Indo-Eurasians [1]. In Europe, there is an increasing prevalence from South to North: in Germany prevalence is 2.2%, in Sweden 10%, and in Estonia 22% [2–4]. There are some gender differences, since rosacea usually starts earlier among females and rhinophyma is almost exclusively seen among males. Ocular involvement is the most common extracutaneous manifestation and affects 6 to 50% of patients with rosacea [5]. In a retrospective investigation from Tunisia, the following frequency was observed in an outpatient dermatologic clinic: erythematotelangiectatic type (12%), papulopustular rosacea (69%), and rhinophyma (3.7%) [6]. This may vary considerably with the type of study and region.

Rosacea is accompanied by stinging and burning sensations of the affected skin. Redness, scaling, pustulation, and phymatous growth are other possible manifestations. Rosacea also has a negative impact on quality of life through stigmatizing feelings and anxiety of patients [7]. Rosacea patients also have an increased risk for cardiovascular disease [8]. In a rapidly growing elderly population in Western countries, rosacea will become an increasing health problem [9].

Although the pathogenesis of rosacea is unknown, there have been a number of recent advances in understanding the disease. Major achievements will be described together with their potential for better treatment for rosacea patients.

Classification of rosacea

Rosacea has been classified into four subtypes [10]. Subtype 1, or erythematotelangiectatic rosacea, is defined by the presence of flushing and central facial erythema. Additional possible features are edema, stinging and burning sensations, as well as roughness or scaling. Subtype 2, or papulopustular rosacea, is defined by persistent erythema and transient papules or pustules. It is a more inflammatory rosacea subtype. Subtype 3, or phymatous rosacea, presents with thickening skin, irregular surface nodularities, and enlargement of affected areas. Areas affected by phymatous rosacea are chin, forehead, cheeks, ears, and nose, with nose or rhinophyma being the

most common phenotype by far with a clear male predominance. Ocular rosacea is defined as subtype 4.

Erythema in rosacea can be subdivided into (a) sole erythema; (b) erythema with telangiectasias; (c) erythema with edema; and (d) erythema with inflammatory papules and nodules. It is of great therapeutic importance to differentiate the perilesional erythema of inflammatory lesions from the diffuse facial erythema [11].

Rosacea and the epidermal barrier function

The clinical observation of a tight association of rosacea with sensitive skin has led to the concept of a disturbed epidermal barrier function in rosacea. A lower irritant threshold corresponds to higher transepidermal water loss (TEWL) and lower stratum corneum hydration. In contrast to atopic dermatitis, the epidermal barrier deterioration in rosacea remains restricted to facial skin [12]. Increased basal TEWL activates certain epidermal proteases, in particular stratum corneum serine proteases [13].

The activation of proteases is the link between impaired barrier function and inflammation in rosacea. The trypsin-like serine protease kallikrein 5 is increased in lesional rosacea. Kallikrein 5 is responsible for the cleavage and activation of cathelicidin LL37—an antimicrobial peptide of skin. In rosacea lesions, both LL-37 and its proteolytic fragments are found in larger amounts than normal [14].

Rosacea and the innate immune system

Toll-like receptors (TLRs) are pattern recognition receptors tightly bound to innate immunity. TLR2 expression is increased in rosacea. This leads to a higher susceptibility of rosacea skin to innate immune stimuli. By activating TLR2, the production of serine proteases in keratinocytes is stimulated [15].

Antimicrobial peptides are part of the innate immune system of human skin. In rosacea, LL-37 levels are remarkably increased—at least in part by TLR2. This may exert various effects related to rosacea pathogenesis and clinical presentation. LL-37 is antimicrobial, pro-inflammatory and angiogenic [16–18].

Various chemokines and cytokines seem to be involved in the inflammatory cutaneous changes of rosacea. Members of the tumor growth factor (TGF) family have been linked to phymatous rosacea. In particular, TGF-β1 and TGF-β2 and the TGF-β receptor type II are overexpressed in phymatous rosacea [19]. A crucial step in chemoattraction of neutrophils is the chemokine CXCL8 induced by LL-37 [20]. Eventually, formation of sterile pustules of subtype 2 rosacea occurs.

Neurogenic inflammation and vascular changes in rosacea

The prolonged flush and persistent erythema are hallmarks of disturbed facial blood flow. Vascular endothelial growth factor (VEGF) is present in epidermis and is expressed by infiltrating cells. VEGF receptor-ligand binding contributes to the vascular changes and cellular infiltration that occurs in rosacea [21]. Another receptor related to local blood flow, vasoactive intestinal peptide (VIP) receptor, is increased in cutaneous blood vessels of phymatous rosacea and in serum [22,23].

Substance P has also been linked to rosacea [24]. This neuropeptide is involved in local blood flow regulation and induces mast cell degranulation leading to increased levels of pro-inflammatory chemokines and cytokines, such as CXCL8, tumor necrosis factor (TNF)-α, and interleukin (IL)-3 [25].

Rosacea skin has a significantly lower heat pain threshold than normal skin. Since transient receptor potential ion channels of the vanilloid type (TRPV)1, and ankyrin 1 (TRPA1) function as cellular sensors for phenomena such as cold and heat, and have a prominent role in pain sensation and inflammation, they are possibly involved in rosacea. The activation of such receptors may increase the release of substance P [26]. A recent study demonstrated that dermal immunostaining of TRPV2 and TRPV3 and gene expression of TRPV1 is significantly increased in subtype 1 rosacea. Subtype 2 rosacea demonstrated enhanced immunoreactivity for TRPV2, TRPV4, and also of TRPV2 gene expression. In subtype 3, rosacea dermal immunostaining of TRPV3 and TRPV4 and gene expression of TRPV1 and TRPV3 was enhanced, whereas epidermal TRPV2 staining was decreased. These data argue for an involvement of TRPVs in rosacea. The different TRPVs have an impact on local immune function, vascular regulation, nociception, and epidermal barrier integrity [27].

Ultraviolet light radiation and rosacea

Ultraviolet light radiation (UVR) is a well-known trigger of rosacea. UVR induces the formation of reactive oxygen species (ROS) in skin [28]. TLR2-ROS interaction leads to increased levels of CXCL8 among other chemokines and cytokines. Furthermore, myeloid differentiation factor MyD88—an adaptor molecule for TLRs—is overexpressed in UV-irradiated and chronic photodamaged skin. It upregulates both IL-6 and matrix metalloproteinase-1 [29].

Demodex mites and rosacea

The human mites *Demodex folliculorum* and *Demodex brevis* are the cause of demodicosis, a disease that can imitate a

variety of other dermatoses, including rosacea. Therefore, it is important to differentiate primary demodicosis from rosacea in order to choose the right treatment option [30].

There has been a long debate on the role of *Demodex* mites in rosacea itself. The prevalence of *Demodex* mites in rosacea patients has been estimated to be as high as 60% (clinically) and 80% (in skin biopsies), with *Demodex folliculorum* as the dominant infestation [31,32]. Increased *Demodex* density in rosacea is considered to be an aggravating factor but not a causative one [33,34].

Treatment of rosacea

The classical approach of rosacea therapy has focused on the inflammatory nodules, pustules and papules. The two most effective topical drugs for rosacea subtype 2 are metronidazole (as gels or ointments) and azelaic acid gel—recently also available as foam [35].

Azelaic acid 15% gel is a topical therapeutic option for subtype 2 rosacea. Azelaic acid reduces ROS, inhibits kallikrein 5 and increases serine protease activity [36,37]. Azelaic acid 15% gel is a US Food and Drug Administration (FDA) approved drug for treating inflammatory papules and pustules in mild to moderate rosacea, due to its anti-inflammatory, anti-oxidant and anti-microbial properties. A newly developed azelaic acid 15% foam formula demonstrated a statistically significant advantage compared to the gel formula in a randomized, double blinded trial with 486 patients over a 12 weeks period, when applied twice daily [38]. A noticeable advantage with azelaic acid foam is that adverse effects (including burning, stinging or itching) were only observed in 10.6% of these participants while 38% of patients using azelaic acid gel had experienced side effects in an earlier trial [39]. The advancement from gel to foam formula may promote more rapid drug penetration and greater total absorption. Foam is becoming increasingly popular with patients due to its ease of application and spread, faster drying time and reduced density, resulting in a higher rate of patient compliance.

Topical metronidazole is of comparable efficacy to azelaic acid gel. It is available as 0.75% gel, 1% gel and 1% ointment. It works as an oxygen scavenger, thereby decreasing ROS and inhibiting neutrophils [40].

Recently, topical ivermectin 1% has been evaluated in two randomized, double-blind, controlled studies for 12 weeks. In both trials ivermectin 1% was superior to the vehicle alone in terms of anti-inflammatory activity and safety [41]. Ivermectin is an anti-helminthic drug and a ligand of farnesoid X receptor, which seems to decrease the density of *Demodex* mites in rosacea skin [42].

Topical calcineurin inhibitors, which inhibit both T-lymphocyte signal transduction and IL-2 transcription, such as pimecrolimus 1% cream and tacrolimus ointment 0.03% or 0.1%, can treat rosacea [43].

Kim *et al.* (2011) investigated the efficacy and safety of 1% pimecrolimus cream for the treatment of rosacea in a 4-week, single-center, open-label study of 1% pimecrolimus (n = 30). The 26 patients who completed the study experienced significantly reduced rosacea clinical scores and mexameter-measured erythema index. The most common side-effects were transient local irritations [44]. Koca *et al.* (2010) compared the effectiveness of 1% pimecrolimus to metronidazole on 48 patients in an open-labeled, randomized, single-center study and found them equally effective [45]. Prospective randomized, multi-center studies have not yet been performed.

Topical calcineurin inhibitors can induce rosacea-like dermatitis and flush, often affecting the cheeks, perioral/perinasal area and forehead/glabellar area [46]. These observations may be explained by propagation of demodicosis due to topical immunosuppression, and drug interactions with alcoholic beverages [46,47].

Skin care products moisturizing the skin, and thereby reducing stinging, burning and the feeling of tightness of skin, are an adjuvant measure. The applications for such adjuvant treatments are subtypes 1 and 2 [48,49]. Some open questions remain. What are the essentials for skin care products in rosacea? Are there cosmetic ingredients with seriously proven efficacy in such patients? So far, no head-to-head studies have been performed to address these questions. Although UVR is a trigger factor for rosacea, there have been no systematic investigations of sun protection.

Oral tetracyclines, like doxycyline and minocycline, have been a cornerstone of systemic treatment in rosacea subtypes 2 and 4. In recent years, the need for an antibiotic effect has been questioned, with regards to rosacea. This has led to the development of a modified-release formulation of anti-inflammatory doxycycline 40 mg given once daily. Time-released formulations of minocycline are also available. It has been shown that tetracyclines decrease matrix metalloproteinase activity involved in kallikrein activation and also act as oxygen scavengers [50,51]. Furthermore, epidermal barrier function improves after tetracycline therapy, as measured by epidermal hydration [52].

Recently, azithromycin has been used to effectively treat ocular and cutaneous rosacea, inhibiting a cluster of pro-inflammatory cytokines (including IL-1, IL-6, IL-8, IL-10, and TNF-α), down-regulating the expression of nuclear factor (NF) kappaB, and inhibiting neutrophil chemoattractant leukotriene B4. Bakar *et al.* (2009) showed that patients who received 500 mg oral azithromycin on three consecutive days, weekly for four weeks, showed significant improvements in their ocular symptoms [53]. Doan *et al.* (2013) further substantiated the effectiveness of azithromycin when their study was performed using 1.5% azithromycin eye drops with 16 children on a median 11 months follow-up. In a single case that did not completely respond, cyclosporine 2% eye drops were added. These investigators stopped azithromycin treatment after 4 to 10 months and there were no recurrences during follow-up [54].

During pregnancy, acute rosacea flare-ups may occur. Fuentelsaz *et al.* described a pregnant woman with rosacea fulminans who was successfully treated after a 3-month tapering course of azithromycin [55], which has been classified as safer than tetracyclines. Whether the dosage, and dosing schedule, of azithromycin may be lowered such that it is sub-antimicrobial but is effective as an anti-inflammatory agent is unclear.

There is some evidence that a combination of topical and systemic therapy might provide better and faster results in initiation therapy, whereas topical treatment is preferred for maintenance [56].

All previous medical treatments failed to improve erythema. Diffuse central facial erythema of rosacea is often chronically present, even in patients who are not experiencing acute flare-ups. Erythema with telangiectasias may improve by laser or intense pulsed light (IPL) therapies [57].

Selective α-adrenergic inhibitors demonstrate vasoconstrictive efficacy. There is extensive clinical experience with brimonidine for glaucoma therapy and with oxymetazoline in rhinitis. Topical α-adrenoreceptor agonists brimonidine and oxymetazoline are now being used to treat rosacea, due to the fact that they target α-adrenoreceptors in the smooth muscle sheath around the cutaneous blood vessels. However, α-agonists have no effect on capillaries and telangiectasias, since they do not contain a smooth muscle layer. Nonetheless, their effects on pre-capillary arterioles do provide significant reduction in the erythema of rosacea [58].

Two phase II trials with topical α2-adrenergic inhibitor brimonidine tartrate, involving 122 and 262 rosacea patients, demonstrated a dose-dependent decrease of facial erythema without rebound or tachyphylaxis. The topical treatment was well tolerated with only mild and temporary adverse effects. The most efficacious formulation was 0.5% brimonidine tartrate leading to significant improvement in 75.5% of patients. Even at the final point of evaluation, the intensity of erythema did not return to the initial baseline level [59]. Systemic exposure to brimonidine tartrate was lower in 0.5% gel formulation than in ophthalmic solution [60]. A one-year open-label study confirmed the consistent efficacy and tolerability of topical treatment, which has gained FDA approval [61]. The resistance to α-adrenergic blockage in about 30% of rosacea patients with moderate to severe erythema is not yet understood. It is possible that other neurovascular mechanisms may be involved.

The α1-selective inhibitor oxymetazoline has been used off-label as 0.05% solution in some cases, but results of clinical trials have yet not been published [62].

Ocular rosacea has a significant impact on quality of life. The treatment of ocular rosacea is based on systemic anti-inflammatory drug therapy, topical therapy with artificial tears, and eyelid hygiene. Once-daily low dose (40 mg) doxycycline is a safe and effective treatment [63]. Cyclosporine A is a calcineurin inhibitor that possesses anti-inflammatory properties. It is capable of inhibiting lipopolysaccharide-induced NF-kappaB activation and acts as an uncompetitive inhibitor of the chymotrypsin-like activity of the 20S proteasome *in vitro* [64]. Cyclosporine A 0.05% ocular emulsion is effective in treating dry eye caused by autoimmune connective tissue disease, and has potential in ocular rosacea as well [65]. Schechter *et al.* (2009) successfully demonstrated the efficacy of a 0.05% cyclosporine A ophthalmic emulsion twice daily for 3 months, on ocular rosacea, in a double-blinded study of 37 patients [66].

A recent alternative to systemic low-dose tetracyclines is topical azithromycin eye drops. The major adverse effect is mild burning after instillation. In a study enrolling 37 patients with ocular rosacea, the necessary treatment time was shorter when compared to systemic doxycycline [67].

There are currently several drugs to treat rosacea in ongoing clinical trials (see Table 1). New potential rosacea drugs may be targeting the TRPVs.

Conclusion

Although we are far away from a complete understanding of the complex pathogenesis of rosacea, there has been much progress in recent times. Treatment tailored to

Table 1: Registered clinical trials for rosacea with medical drugs [68]

NCT-No.	Drug(s)
NCT01125930	atralin gel (tretinoin 0.5%)
NCT01045551	apremilast
NCT01134991	topical minocyline foam

specific rosacea subtypes has been incorporated in clinical guidelines. The importance of differential diagnosis of perilesional and persistent facial erythema is evident. Rosacea therapy has become effective, safer and for the first time includes a medical approach to improve persistent erythema.

With further investigations into the biochemical pathways specifically uncovering the key mediators of inflammation, more effective and potent drugs can control the condition, change its natural history, and perhaps induce a remission or cure.

Abbreviations

FDA, US Food and Drug Administration; IL, interleukin; IPL, intense pulsed light; NF, nuclear factor; ROS, reactive oxygen species; TEWL, transepidermal water loss; TGF, tumor growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TRP, transient receptor potential ion channel; TRPV, transient receptor potential ion channel of the vanilloid type; UVR, ultraviolet light radiation; VEGF, vascular endothelial growth factor.

Disclosures

The author declares that he has no disclosures.

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