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Review

Advances in the Pathogenesis and Treatment of Rosacea: A Phenotype-Based Therapeutic Approach

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Abstract: Rosacea is a common chronic inflammatory skin disorder that mainly affects the central face. It is primarily characterized by recurrent episodes of flushing, persistent erythema, inflammatory papules, telangiectasias, phymatous changes, and ocular symptoms. Its pathogenesis is complex and still not completely understood. It encompasses innate and adaptive immune system dysregulation, neurovascular dysfunction, and genetic and environmental factors. To date, four subtypes of rosacea have been identified, based on the predominant clinical features: erythemato-teleangiectatic, papulopustular, pyhomatous, and ocular rosacea. New insights into this condition have led to several pharmacological treatments, including topical medications, spanning from the conventional azelaic acid, metronidazole, benzoyl peroxide, clindamycin, and erythromycin to new ones including not only brimonidine, oxymetazoline, ivermectine, and minocycline but also systemic drugs such as oral antibiotics, isotretinoin, non-selective β-blockers or α2-adrenergic agonists, and laser- or light-based therapies, together with new therapeutic approaches. The aim of this study was to review the current literature on the pathophysiology of rosacea and to provide an overview of therapeutic approaches that specifically address each clinical subtype.

Keywords: rosacea; subtypes; pathogenesis; treatment

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1. Introduction

Rosacea is a chronic inflammatory skin disorder with a relapsing course that primarily affects the centrofacial and periocular regions. It is characterized by recurrent episodes of flushing, persistent erythema, inflammatory papules, and telangiectasias [1]. Most patients with rosacea also experience ocular involvement, such as blepharoconjunctivitis with eyelid margin inflammation and meibomian gland dysfunction [2]. The disease is oftentimes associated with systemic comorbidities, such as hypertension, dyslipidemia, inflammatory bowel disease, and psychiatric comorbidities, namely anxiety and depression [3,4]. For these reasons, it is not surprising that rosacea has a substantial impact on patients' quality of life [5] and consequently society and healthcare expenditure [6].

From an epidemiological point of view, rosacea represents a common dermatological disorder with a slight female predominance and a worldwide prevalence of approximately 5% of the general population [7].

Although the real nature of rosacea remains largely elusive, it is known that its pathogenesis encompasses a complex interplay between innate and adaptive immune system

dysregulation, neurovascular dysfunction, and genetic and environmental factors [8]. To date, most evidence points towards several triggering factors that may initiate or worsen the disease, including ultraviolet (UV) exposure, local inflammation responses to skin microorganisms (Demodex mites), temperature changes, and stressors [9].

In 2002, the National Rosacea Society Expert Committee (NRSEC) proposed classification of the disease into four categories: erythemato-teleangiectatic, papulopustular, pyhomatous, and ocular rosacea [10]. This classification underwent a revision in 2016 because of new insights into the pathogenesis of rosacea, obtained by establishing a new approach for diagnosis and classification of rosacea based on disease phenotype [11]. Recent findings have suggested that erythemato-telangiectatic and papulopustular rosacea are the most common patterns within the four subtypes, with no differences between the sexes except for the phymatous one, which seems to be more prevalent in men [12].

Despite the burden of rosacea in dermatological clinics, treatment options, which include topical and oral therapies, light devices, skin care, and lifestyle management, often yield poor results [13]. To date, all therapeutic strategies mainly aim to control the clinical symptoms rather than target the causes or prevent the disease.

For all of these reasons, managing rosacea still represents a real challenge for dermatologists, since the choice of the most appropriate treatment strategy not only relies on the clinical characteristics of rosacea lesions but also the patient's reported symptoms and preferences and the physician's experience.

The aim of our paper was to review the current literature on the pathophysiology of rosacea and to provide an overview of therapeutic strategies and approaches that specifically address each clinical subtype of rosacea.

2. Pathophysiology

Rosacea is characterized by a multifactorial pathophysiology, resulting from the interaction between environmental influences, genetic factors, immunological, vascular, and neuroinflammatory dysregulation, and the impairment of skin barrier function. A schematic illustration of the main factors playing a role in the pathogenesis of rosacea is shown in Figure 1.

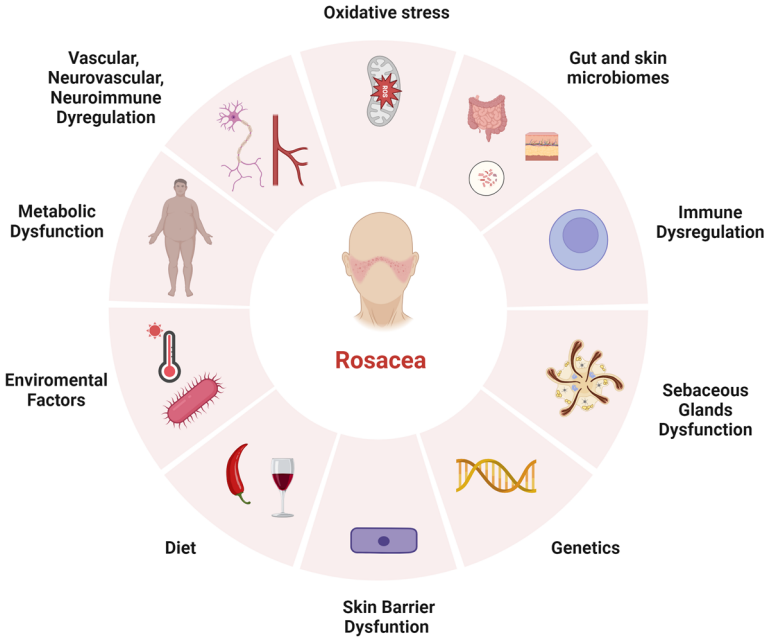

Figure 1. Schematic illustration of the main factors playing a role in the pathogenesis of rosacea.

2.1. Environmental Factors

Several environmental factors have been recognized in the initiation or aggravation of rosacea. The association between Demodex mites and the disease is well-known, although

the underlying pathogenic mechanisms are still unclear [14]. Demodex follicolorum, a commensal of human skin that mainly colonizes hair follicles, is five to seven times increased in skin biopsies of patients with rosacea [15], particularly in the papulopustular and phymatous subtypes [16,17]. In addition, resident bacteria such as Bacillus oleronius and Staphylococcus epidermidis may worsen the inflammatory reaction by inducing chemotaxis of innate immune cells, such as neutrophils [18]. Dietary habits may play a role in inducing rosacea. In detail, heat, alcohol, capsaicin, and histamine- and cinnamaldehyde-related foods may activate transient receptor potential (TRP) cation channels, resulting in neurogenic vasodilatation, inflammation, and oxidative stress dysfunction [19]. Finally, emotional stress can affect, reveal, or amplify rosacea features by modulating the hypothalamic–pituitary–adrenal axis (HPA) and releasing neuropeptides, neurotrophins, and lymphokines from nerve endings and dermal cells [20].

2.2. Genetic Predisposition

The genetic basis of rosacea is still poorly understood, although family inheritance, twin concordance, and associations with other autoimmune disorders may attest to a genetic predisposition to this skin condition [21]. A null mutation polymorphism in glutathione S-transferase (GST), which plays a key role in cellular defense against electrophilic chemical species and reactive oxygen species (ROS), has been reported in patients with rosacea [22]. Other significant gene polymorphisms include human leukocyte antigen (HLA) class II [23], tachykinin 3 receptor (TACR3) [24], vitamin D receptor (VDR) [25], and vascular endothelial growth factor (VEGF) [26]. Interestingly, Deng et al. [27] presented the integrated results of whole-genome sequencing (WGS) and whole-exome sequencing (WES) in Chinese rosacea families. In their study, the authors identified single rare deleterious variants of LRRC4, SH3PXD2A, and SLC26A8 genes that are linked to neural function, data which support the familial inheritance of neurogenic inflammation in rosacea development [27].

2.3. Immune Dysregulation

Innate immunity is a key player in the initiation and maintenance of rosacea. The dysregulation of toll-like receptor (TLR)2-kallikrein (KLK5)-cathelicidin(LL37) pathways has a crucial role in the pathogenesis of rosacea [28]. TLRs, type I integral transmembrane glycoproteins involved in host cell recognition and responses to microbial pathogens, are among the most characterized innate immune receptors [29]. TLR2 is a member of the TLR protein family, widely expressed in immune, endothelial, and epithelial cells, including keratinocytes and fibroblasts [30]. Following the interaction between pathogen-associated molecular patterns (PAMPs), TLR2 promotes a complex cascade of intracellular signaling [31] that leads to the activation of nuclear factor B (NFκ-B) and the release of proinflammatory cytokines, mainly interleukin (IL)-1, tumor necrosis factor α (TNFα), IL-6, thymic stromal lymphopoietin (TSLP), chemokines, matrix metalloproteinase, and prostaglandins [32]. In addition, TLR2 activation is associated with the release of KLK5, a critical protease involved in the pathogenesis of rosacea [33]. Although the upstream stimulator of TLR2 in rosacea is still unknown, keratinocytes of rosacea patients express higher amounts of this protein than healthy individuals. This fact may partially explain the overreactive response to environmental stimuli [34]. Furthermore, rosacea is associated with increased levels of KLK5, although the ultimate effect of this pathway depends on the cleavage of the active form of the antimicrobial peptide LL-37 [30]. KLK5 is not only involved in the innate immune system within the skin through LL-37 but is also able to directly activate protease-activated receptor 2 (PAR2), triggering the expression of pro-inflammatory cytokines such as IL-8 [35]. The production of LL-37 has been linked to different cell types, including mast cells, which are particularly increased in rosacea lesions [36–38]. Interestingly, subcutaneous injections of LL-37 have induced a strong inflammatory response in skin mouse models [33], while telangiectasia, erythema, and inflammation were not featured in mast cell-deficient mice, emphasizing the role of mast cells in the pathologenesis of rosacea [39]. Notably, LL-37 also promotes the release of

matrix metalloproteinase (MMP)-9, which in turn activates KLK5, amplifying LL-37 expression, and perpetuating a vicious circle where inflammation is maintained [30]. However, further translational research validating molecular mechanisms in humans is still needed in this field. The complex immunomodulatory role of LL-37 is driven by multiple pathways [40]. Interestingly, LL-37 activates the Janus kinase (JAK)/signal transducer and transcription activator (STAT) signaling pathway, which mediates monocyte chemotaxis and IL-6-, IL-8-, and TNFα expression [41]. Downstream, LL37 exerts its effect through the NFκB pathway which promotes the release of proinflammatory cytokines and chemokines through mTORC1 signaling, which is hyperactivated in rosacea patients. In a positive feedback loop, mTORC1 leads to the activation of LL-37, which in turn activates mTORC1 signaling by binding TLR2 [42,43]. Finally, TLR2 also facilitates the activation of nucleotide binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3), a component of the NLRP3 inflammasome complex, in keratinocytes, which contributes to orchestrating neutrophil chemiotaxis, TNFα-mediated inflammation, prostaglandin e2 synthesis, and IL-1 cleavage and activation [44]. Interestingly, as with other inflammatory skin diseases, evidence is emerging of the role of the IL-1 family of cytokines in rosacea [45].

Both T and B lymphocytes are thought to contribute to the pathogenesis of rosacea, although little is known of the role of adaptive immunity. Histological analysis has revealed predominantly CD4+ T cells around the follicular and perivascular regions in rosacea skin [46]. The T-cell response in all rosacea phenotypes is mainly driven by Th1/Th17-polarized immune cells, as demonstrated by significant upregulation of their cytokines IFN-γ, TNF, IL-17, and IL-22 [47]. Moreover, Th17 promotes vascular endothelial growth factor (VEGF) expression in rosacea, which is also associated with angiogenesis [48]. Recent evidence has pointed to the role of activated B cells, as testified by high levels of B cell markers in skin biopsies of rosacea patients [47]. Additionally, B lymphocytes are responsible for the production of fibrogenic cytokines, such as IL-6 and transforming growth factor beta (TGFb), implicated in the fibrotic changes in phymatous rosacea [8].

2.4. Vascular, Neurovascular, and Neuroinflammatory Dysregulation

Comprehensively, increased skin blood flow, angiogenesis, and vasodilatation are essential processes in rosacea, as demonstrated by typical clinical features such as facial erythema and flushing [13]. The face is one of the few regions of human skin where blood vessels are simultaneously regulated by the sympathetic, parasympathetic, and sensory nerves; thus, vascular dysregulation is the result of a complex interaction. As already mentioned, VEGF and LL-37 are upregulated in rosacea, causing increased vascular permeability, angiogenesis, and vasodilatation [48]. Overall, the pro-angiogenic role of LL-37 is exerted via activation of the formyl peptide type 1 (FPR1) receptor, epidermal growth factor receptor (EGFR), and downstream signaling in epithelial cells [9]. In addition, LL-37 enhances the expression of the adhesion molecules intracellular adhesion molecule-1 (ICAM1), vascular cell adhesion molecule-1 (VCAM-1), and VEGF expression, which actively contribute to the regulation of angiogenic processes [49,50]. Neuroinflammatory and neurovascular dysregulation are also linked to facial erythema, edema, and hyperemia in rosacea patients [51]. The proximity between immune cells in the skin barrier and peripheral nervous system nerves may partially explain the intensive bidirectional crosstalk between those systems through different mediators. Notably, patients with rosacea are susceptible to several stimuli, including UV radiation, cold, heat, or stress, suggesting the relevance of the sensory nervous system in the pathogenesis of rosacea [52]. In detail, TRP ion channels include 27 related molecules that respond to a remarkable variety of chemical and physical factors and are linked to both pro- and anti-inflammatory mechanisms [53]. They are considered important components of the sensory system, mainly located on neuronal and non-neuronal cells, including mast cells, dendritic cells, endothelial cells, and keratinocytes [54]. High numbers of TRP channels seem to be responsible for transducing thermal, chemical, and mechanical rosacea stimuli into clinical manifestations of rosacea. Via the influx of cations, TRP channels lead to the release of vasoactive neuropeptides,

such as substance P (SP), the peptide linked to the calcitonin gene (CGRP), the activator polypeptide of l pituitary adenylates cyclase (PACAP), the vasoactive intestinal peptide (VIP), or even bradykinin, which is involved in rosacea associated vasodilation, plasma extravasation, and leukocyte recruitment [55]. Moreover, TRP channels mediate pain sensations and itching [56]. Specifically, the activation of TRP ankyrin type 1 (TRPA1) and TRP vanilloid type 1 (TRPV1) lead to a burning sensation and flushing in rosacea patients [57].

2.5. Other Contributors (Sebaceous Glands, Skin Barrier Dysfunction, and Microbial Dysbiosis)

The sebaceous glands are exocrine glands that produce sebum, a lipid-rich fluid, produced by the holocrine rupture of mature sebocytes and secreted onto the surface of the skin. Sebaceous glands are mainly located on the face, scalp, chest, and back, and their dysfunction has been observed in several dermatological conditions, including acne and rosacea [58,59]. In particular, phymatous rosacea has been associated with thickening of the skin due to sebaceous gland hyperplasia [30]. Interestingly, the role of those glands has emerged from several studies on rosacea patients in which topical isotretinoin resulted in a significant reduction in sebaceous gland volume and sebum production, as well as in improvement of erythema and papulo-pustules [60]. Notably, the sebaceous fatty acid profile in patients with rosacea shows a decrease in long-chain saturated fatty acids that leads to skin dryness and hypersensitivity [61]. In this context, sebocytes could contribute to the general inflammatory status by releasing proinflammatory cytokines and adypokines, including IL-6 [8]. Although the pathophysiological link between chronic inflammation and glandular hyperplasia remains elusive, sebaceous gland dysfunction in rosacea might arise from TLR-mediated inflammatory status, changes in the skin microbiome, alteration in neuronal and endocrine factors, and alteration in skin barrier permeability [62].

Skin integrity is crucial since the skin acts as a barrier to microbes, toxins, and physical stressors, including UV radiation. The stratum corneum and tight junction are two important factors that contribute to maintaining balance in the epidermal barrier [63]. The dryness and hypersensitivity of rosacea skin may be attributed to a reduction in the hydration of the stratum corneous, also due to the decrease in claudin expression, a tight junction membrane protein which forms paracellular barriers and pores, determining tight junction permeability [64]. Indeed, molecular dysfunction in claudin expression has been observed in patients with papulopustular rosacea [62].

Furthermore, an intriguing link between the cutaneous microbiome and rosacea has been described [65]. An imbalance in common skin bacterial species, such as Cutibacterium acnes, Staphylococcus epidermidis, Bacillus oleronius, and Demodex folliculorum, might play a central role in rosacea pathogenesis, through propagation of the inflammation response [66]. However, the microbiological reverberations are not only limited to the skin, but surprisingly, emergent studies have described a potential interplay with the gut microbiome, although the exact mechanisms are still unknown [67,68].

Finally, the association between rosacea and several metabolic conditions, including hypertension, dyslipidemia, obesity, thyroid disorders, and diabetes, has been widely demonstrated in the literature [69–71]. Based on current knowledge, rosacea and metabolic-related disorders share increased levels of cathelicidin and inflammatory cytokines, which are responsible for the pathogenesis of both diseases [72].

3. Classification

The diagnosis and classification of rosacea was historically based on the predominant clinical features, which identified four disease subtypes: erythemato-telangiectatic, papulo-pustular, phymatous, and ocular rosacea [10,73]. Representative clinical pictures for each rosacea subtype are shown in Figure 2. As multiple features tend to present simultaneously and rosacea features can span multiple subtypes, a new phenotype-based approach was then proposed to facilitate clinical practice and improve rosacea management [11]. Indeed, this “phenotype” approach may address rosacea and its treatment in a manner that is more

accurate and consistent with the patient's individual experience. Thus, according to the National Rosacea Society [11], two features are considered as independently diagnostic for rosacea: (i) persistent, centrofacial erythema associated with periodic intensification and (ii) phymatous changes. In addition, minor features include a burning or stinging sensation, erythematous plaques, facial dryness and scaling edema, a peripheral location, and ocular manifestations [11].

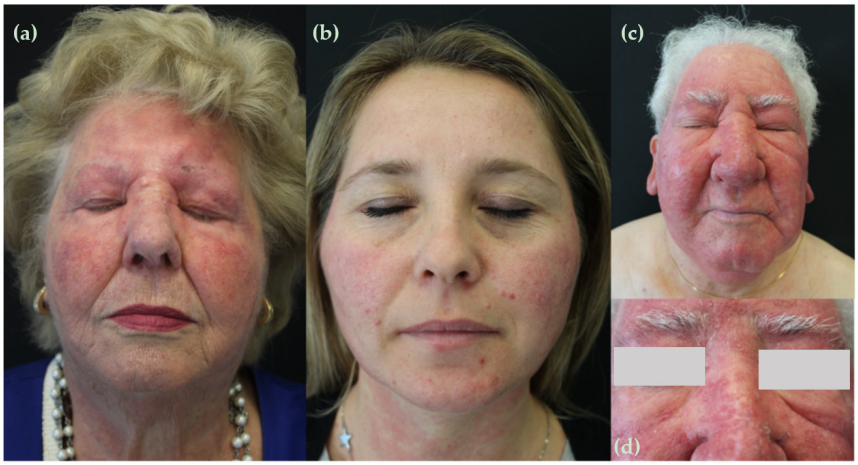

Figure 2. Erythemato-telangiectatic rosacea (**a**) is characterized by flushing, persistent centrofacial erythema, and telangiectasias. Papulopustular rosacea (**b**) is defined by erythema with a centrofacial distribution, with typically small (<3 mm) erythematous papules and/or pustules, both occurring singly or in clusters and at different stages of development. In more severe forms, inflammatory plaques or oedema may be present. Hypertrophy of the sebaceous glands and connective tissue is the hallmark of phymatous rosacea (**c**). The predominant form is rhinophyma, which occurs mainly in males and results in skin thickening with a nodular appearance, along with telangiectasias. This subtype may involve the chin (gnathophyma), forehead (metophyma), ears (otophyma), and eyelids (blepharophyma). Ocular rosacea (**d**), which may overlap with other subtypes, causes telangiectasia of the eyelid margin, conjunctival injection, blepharitis, and occasionally ectropion.

4. Treatments

Currently, several treatment options have been approved for rosacea, although considerable differences may be observed within rosacea subtypes [74,75]. Nevertheless, the identification and avoidance of triggering factors (e.g., alcohol, the sun, hot drinks and spicy food) [75], self-care advice, and general skin care measures (e.g., mild facial cleansers and high-SPF broad-spectrum physical sunscreen) [13] remain fundamental for the proper management of all rosacea patients, leading to better treatment results [76]. The key aspects of the phenotype-based therapeutic approaches in rosacea are summarized in Table 1.

Table 1. Key aspects of a phenotype-based approach in rosacea.

Rosacea Subtype	First Line Therapies	Alternatives
Erythemato-telangectatic	• Topical brimonidine tartrate 0.5% gel or oxymetazoline hydrochloride 1% cream for persistent facial erythema. • IPL, PDL, and Nd:YAG laser for persistent facial erythema and telangectasia.	• Topical metronidazole, azelaic acid, or calcineurin inhibitors in the case of co-existent inflammatory lesions. • Oral non-selective β-blockers carvedilol or α2-adrenergic agonist clonidine to decrease erythema and flushing. • Intradermal injection of botulinum toxin A in resistant conditions.

Table 1. *Cont.*

Rosacea Subtype	First Line Therapies	Alternatives
Papulopustular	• Topic azelaic acid (15% gel or 20% cream and 15% foam), metronidazole (0.75% gel, cream, and lotion and 1% cream and gel), or ivermectin (1% cream). • Oral subantibiotic-dose doxycycline 40 mg modified release capsule. Alternatively, tetracycline and minocycline. • Intermittent courses of oral low-dose isotretinoin (0.2 mg/kg/day) in the case of antibiotic failure or to avoid long-term therapies.	• Minocycline 1.5% foam, topical retinoids (adapalene 0.1% gel and tretinoin 0.025% cream) and topical antibacterial (clindamycin, erythromycin. and benzoyl peroxide) for more severe or recalcitrant rosacea. • Erythromycin, azithromycin, and clarithromycin in patients not eligible for tetracyclines. • Nd:YAG laser for persistent or severe cases.
Phymatous	• Nasal debulking through surgical approaches or laser ablation.	• Consider oral isotretinoin to prevent relapse after surgery.
Ocular	• Proper lid hygiene and ocular lubricants. • In the case of persistent symptoms, refer to ophthalmology. • Cyclosporine, azithromycin, or tacrolimus as topical agents.	• Oral subantibiotic-dose doxycycline. • IPL for evaporative dry eye disease with meibomian gland dysfunction.

4.1. Transient/Persistent Centrofacial Erythema and Telangiectasia

To date, different therapeutic strategies are available for the treatment of flushing and facial erythema, including topical, systemic, or combined approaches; with regard to telangiectasias, vascular lasers and light-based therapies should be preferred [77].

Among the topical treatments, brimonidine tartrate (BT) topical gel is a highly selective α2 agonist approved for moderate-to-severe subtype I rosacea that induces the vasoconstriction of small arteries and veins, reducing vasodilation and edema. Applied once daily, its effects can be reached within 30 min with maximal mitigation in erythema 3–6 h after administration [78]. From two multicentric randomized trials, it emerged that after 1 month of therapy, there was a significant improvement in erythema after the application of brimonidine gel 0.5% in patients with erythemato-telangiectatic rosacea, but it did not significantly affect dilated capillaries [79]. Interestingly, Moore et al. [80] focused on the long-term safety and efficacy of topical BT gel 0.5% applied once a day for 12 months. They found that the most common adverse effects in their patients were flushing (9.1%), followed by worsening erythema (6.5%) and rosacea (3.6%), with the highest efficacy at months 1–3.

Oxymetazoline hydrochloride 1% cream represents another topical option for erythemato-telangiectatic rosacea. It is a potent α-1-adrenergic agonist that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of persistent erythema in adult patients [81]. Indeed, the results of the REVEAL study, conducted on 440 patients, demonstrate the safety and continued efficacy of oxymetazoline cream 1.0% for moderate-to-severe persistent erythema, although redness may flare after the discontinuation of treatment [82]. Moreover, 8.2% of the entire cohort reported treatment-emergent adverse events (TEAEs), including application-site dermatitis, paresthesia, pain, and pruritus [82]. Moreover, no clinically meaningful changes were observed in skin blanching, inflammatory lesions, or telangiectasia [82].

Several clinical trials on topical calcineurin inhibitors in papulopustular rosacea, such as pimecrolimus and tacrolimus, have shown excellent results in reducing the erythematous inflammatory component [83,84], even in the steroid-induced form of rosacea [85,86]. Conversely, Zhang et al. [87] underline a possible negative effect of pimecrolimus and tacrolimus since these drugs can even induce paradoxical rosacea-like eruptions.

Finally, a few studies have demonstrated that topical metronidazole and topical azelaic acid may reduce erythema in rosacea patients, although their efficacy has only been demonstrated in patients suffering from the papulopustular subtype [88–90].

Concerning oral therapies, the role of vasoactive compounds is still controversial. Nonselective β-blockers, especially carvedilol, are thought to decrease erythema and flushing, as well as α2-adrenergic agonist clonidine [91,92]. However, evidence supporting their efficacy is still limited.

Vascular lasers and light-based therapies remain one of the most effective strategies for persistent vascular manifestation, including erythema and telangiectasia. Intense pulsed light (IPL), pulsed dye laser (PDL), and neodymium:yttrium–aluminum–garnet laser (Nd:YAG) are recommended for erythemato-telangiectatic rosacea [93].

IPL has a wavelength between 420 and 1200 nm, which is absorbed by melanin and oxyhemoglobin [94]. Using filters, it emits the required wavelength to target vessels, minimizing energy absorption by melanin, which is not a desired target in rosacea, thus avoiding side effects such as hypopigmentation. This technology works by collating vessels, remodeling collagen, and reorganizing connective tissue [95]. Longer wavelengths are effective for deeper vessels, while shorter ones target more superficial vessels but can interact with melanin and should be avoided in darker skin types [96]. Generally, at least three sessions are required, at intervals of 1–3 weeks, and IPL can be used both in monotherapy and in combination with bipolar radiofrequency [97]. Interestingly, Papageorgiou et al. [98] reported a significant improvement in erythema and telangiectasia after four treatments performed at 3-week intervals, with self-limiting side effects. As regards a PDL, this device emits light in the wavelength of 585–595 nm, with the absorption peak of oxyhemoglobin targeting the superficial capillaries, leading to the obstruction of blood vessels. Used at purpuragenic fluences, it can provide a significant improvement in erythema, symptoms, and quality of life [99], especially in thick, rope-like telangiectasias [100]. Notably, to avoid post-treatment purpura and dyspigmentation of the earlier generation PDLs, a long-pulsed (595 nm) PDL at subpurpuric fluences can be used, with a very favorable safety profile [101]. In addition, fine and superficial telangiectasia seem to respond well to a potassium titanyl phosphate 532 nm laser (KTP laser), although PDL treatments have shown better outcomes [102]. Compared to the microsecond 1064 nm Nd:YAG, the non-purpuragenic 595 nm PDL was more effective for facial erythema in lighter-skinned patients, but microsecond Nd:YAG resulted in being less painful [103]. The synergistic approach to laser therapy, conducted through a sequential delivery of 595 and 1064 nm wavelength radiation with an interpulse delay, has proven to be more effective than standard single-wavelength therapy for facial telangiectasia [104].

In conclusion, patients with prominent telangiectasia will significantly benefit from laser/light-based therapies, but the in case of prominent underlying erythema, which may impair the discrimination of telangiectasia, combination therapies can also be used. Micali et al. [105] proposed a combined approach of sequential treatment for patients showing both marked background erythema and marked telangiectasias. Complete clearing of facial erythema was reached with a session of Nd:YAG laser followed by a first application of brimonidine and a second application 1 month after laser treatment [105].

Moreover, adjuvant topical brimonidine can be used to reduce IPL-induced erythema and associated pain without affecting efficacy [106].

Something that is noteworthy is that another emerging procedural therapy for both erythemato-telangiectatic and papulopustular rosacea is topical photodynamic therapy with 5-aminolevulinic acid (ALA-PDT). It has proved to be safe and effective [107], also in combination with IPL [108]. Lastly, two sessions of fractional microneedling radiofrequency (FMR) treatment at 4-week intervals showed modest improvement in erythema, and it might be used as an alternative or in combination with other treatment methods [109].

An intradermal injection of botulinum toxin (BTX) in large dilution (2 U/0.1 mL, with a total of 20 units of BTX) has recently been used off-label in erythemato-telangiectatic rosacea resistant to previous treatments, with the aim of reducing flushing, erythema, and

inflammatory lesions [98]. BTX blocks the release of acetylcholine from the peripheral autonomic nerve endings of cutaneous vessels, thus reducing vascular disease manifestations [99]. Also, it may block the effects of acetylcholine on the erector muscles of the hair and the muscarinic receptors of the sebaceous glands [100]. Finally, BTX inhibits the release of substance P and the calcitonin gene-related peptide, reducing skin inflammation [101]. Interestingly, several studies have reported good outcomes for transient and persistent erythema in patients treated with a different subtype of botulin type A (BTX-A), including onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A [102–104].

4.2. Papulopustular Rosacea

Generally, papulopustular rosacea patients show a rapid response to topical medications, including azelaic acid, metronidazole, ivermectin, benzoyl peroxide, clindamycin, and erythromycin [110]. Even though for many years systemic therapies were preferred only for refractory patients, with the introduction of tetracyclines, oral therapy has become more commonly prescribed as a first-line treatment, alone or more often in combination with topical therapies [111].

As regards topical therapies, azelaic acid (AA) is a natural nine-carbon straight-chain saturated dicarboxylic acid widely found in barley, wheat, and rye and produced by Malasezzia furfur [112]. Due to its anti-inflammatory, anti-microbial, antioxidant, anti-comedolytic, and antikeratinization activities, AA is indicated for acne, rosacea, melasma, and other dermatological conditions [113]. Topical 15% gel is approved by the Food and Drug Administration for inflammatory papules and pustules in mild-to-moderate rosacea, given its role in reducing ROS production and proinflammatory cytokines (including IL-1, IL-6, and TNFα). Also, it inhibits KLK5 and cathelicidin, and increases serine protease activity [114,115]. A recent meta-analysis demonstrated that erythema intensity and inflammatory lesion counts significantly improved in rosacea patients treated with AA compared with a vehicle after 12 weeks [116]. Moreover, a randomized trial showed that the use of 15% azelaic acid gel twice daily for 15 weeks has higher efficacy compared to 0.75% metronidazole gel, particularly regarding the inflammatory features of rosacea [117]. Another possible formulation of AA is the 20% cream, which seems more effective in papulopustular rosacea [118]. Finally, AA foam 15% is an effective and well-tolerated option that matches the needs of all skin types [119].

Metronidazole (MTZ) is a nitroimidazole antibiotic approved for papulopustular rosacea [120]. It is available in different formulations (as a gel, cream, or lotion). Usually, 0.75–1% cream and gel are the most used treatments. Traditionally applied twice daily, recent evidence has demonstrated that both 0.75% metronidazole cream and 1.0% metronidazole cream used once daily can provide well-tolerated efficacy for moderate-to-severe rosacea [121]. Topical metronidazole gel can also be used in combination with oral therapies, and the prolonged use of gel alone has shown a significantly high disease-free interval and lower recurrence [122]. Compared to AA, MTZ may have a higher tolerable profile, even though 15% azelaic acid gel twice daily for 15 weeks demonstrated significant superiority over 0.75% metronidazole gel in reducing inflammatory lesions and erythema [117].

Ivermectin is a broad-spectrum antiparasitic agent, recently introduced as a topical therapy for papulopustular rosacea, and, in particular, it targets the Demodex mite [123,124]. It also exerts an anti-inflammatory effect, since it upregulates the anti-inflammatory cytokine IL-10 and decreases IL-1β, TNFα, and neutrophilic diapedesis [125]. The application of ivermectin cream 1% once a day has shown clinical superiority and higher patient satisfaction over metronidazole cream 0.75%/twice daily [126].

Other topical therapies include treatments that have been mainly used for acne vulgaris in clinical practice. Despite its therapeutic properties, topical benzoyl peroxide (BPO) in patients with rosacea has traditionally been avoided due to high irritation rates. The FDA recently approved 5.0% microencapsulated benzoyl peroxide (E-BPO) for papulopustular rosacea. This encapsulation forms a barrier between the drug and the skin, with gradual release and the absorption of BPO, reducing tolerability issues and adverse events [127]. A

12-week treatment with minocycline 1.5% foam showed efficacy for moderate-to-severe papulopustular rosacea, maintaining a favorable safety profile without serious treatment-related adverse events [122]. A study conducted on calcineurin inhibitors demonstrated a reduction in facial erythema, although no significant decrease in the number of papulopustular lesions was observed [123]. Regarding topical retinoids, a randomized open trial with 55 rosacea patients demonstrated the efficacy of adapalene gel 0.1% [124]. Additionally, in a randomized double-blind trial, topical tretinoin 0.025% cream appeared to be effective for severe or recalcitrant rosacea compared to low-dose oral isotretinoin [125]. However, retinoids are usually avoided due to their irritant potential. Lastly, clindamycin and erythromycin in cream/gel have also shown good results, but larger studies still need to be carried out [126].

Oral antibiotics and isotretinoin represent the first line agents in severe papulopustular rosacea forms. Tetracyclines and their second-generation semisynthetic derivatives have anti-inflammatory properties and have proven to be effective in the treatment of inflammatory skin conditions [128]. Their primary mechanism of action against bacteria derives from their ability to bind to the bacterial 30S ribosomal subunit, thus inhibiting protein synthesis [128] and reducing inflammation [129]. Also, tetracyclines can exert anti-inflammatory and antioxidative activities by downregulating inflammatory cytokines, leukocyte migration, chemotaxis, and ROS production, as well as antiangiogenic effects via matrix metalloproteinase inhibition. These drugs also showed inhibitory effects on granuloma formation and proteolysis [130–132]. The only oral tetracycline approved by the FDA for moderate-to-severe papulopustular rosacea is a subantibiotic dose doxycycline 40 mg modified release capsule once daily [133]. This anti-inflammatory dose of doxycycline is as effective as a standard dose of 100 mg and offers the advantages of increased bioavailability, no bacterial resistance, and candidiasis [134], as well as minimal gastrointestinal side effects [135]. Of note, good and faster effects can be achieved by combining oral modified-release doxycycline (40 mg once/day) and AA 15% or MTZ 1% gel [136]. Oral minocycline 100 mg may represent a good alternative, since it was demonstrated that over a 16-week treatment period, 100 mg of minocycline was non-inferior to 40 mg of doxycycline in terms of efficacy, with comparable safety profiles [137]. Among the emerging tetracycline-derived antibiotics used for acne, lymecycline could also find greater application for the treatment of rosacea and topical steroid-induced rosacea [138,139].

Erythromycin, azithromycin, and clarithromycin have been used effectively and safely for the treatment of papulopustular rosacea, especially in patients not eligible for tetracyclines due to pregnancy, allergy, or intolerance or in cases of a lack of response [140]. Indeed, the management of pregnant women with inflammatory skin diseases is oftentimes challenging. Erythromycin in doses of 250–1000 mg/day is generally used in pregnant women with rosacea [141]; clarithromycin and azithromycin have been shown to have a faster effect with less gastrointestinal distress than erythromycin [142]. Generally, macrolides are considered second-line antibiotic therapies given the high rate of resistance that they have developed in recent years [143]. Furthermore, a double-blind trial (n = 29) showed the superiority of oral metronidazole compared to a placebo after 6 weeks of treatment [141]. Moreover, oral metronidazole (250 mg thrice daily for two weeks) can be added to oral minocycline (50 mg twice daily) to reduce relapses in rosacea patients, with a good safety profile [142].

For severe or antibiotics-recalcitrant papulopustular rosacea, intermittent courses of oral low-dose isotretinoin have also been reported to be effective, due to its anti-inflammatory properties. Oral low-dose isotretinoin (0.2 mg/kg/day) showed superiority compared to a placebo after 4 months of treatment of difficult-to-treat papulopustular rosacea [144]. In another controlled trial, low-dose oral isotretinoin was more effective than a placebo and acted like doxycycline (0.3 mg/kg/day) [145].

A systematic review focused on the widely spread notion that systemic isotretinoin taken within 6 to 12 months of cutaneous surgery could contribute to abnormal scarring or delayed wound healing. In this study, insufficient evidence was found to support

delaying cutaneous surgery and most dermatological procedures, except for mechanical dermabrasion and fully ablative laser, which are not recommended in the setting of systemic isotretinoin treatment [146]. Interestingly, combined treatment of recalcitrant papulopustular rosacea involving PDL and fractional microneedling radiofrequency with low-dose isotretinoin demonstrated satisfactory efficacy with reasonable safety profiles in 25 patients with rosacea [147].

In an open clinical trial, the Nd:YAG laser was shown to be safe and effective against papulopustular lesions [145].

Interestingly, novel monoclonal antibodies and oral JAK inhibitors, largely used for the treatment of other inflammatory skin conditions such as psoriasis or atopic dermatitis, have also shown certain degrees of efficacy in papulopustular rosacea [146,147].

In an exploratory, open-label, investigator-initiated clinical trial, secukinumab, a human monoclonal antibody anti-interleukin-17A, led to a significant reduction in both papule count and global severity score (GSS) in patients with moderate-to-severe papulopustular rosacea [148]. Moreover, a recalcitrant case of granulomatous rosacea resolved after subcutaneous injections of adalimumab, a TNFα inhibitor, thus demonstrating the therapeutic potential of this agent for this condition [149].

Finally, a case series of patients with erythemato-telangiectatic and papulopustular rosacea treated with the oral JAK inhibitor tofacitinib was published, with it showing significant regression of rosacea signs and symptoms [150].

4.3. Phymatous Changes

Rhinophyma, a hypertrophy of the nasal soft tissues, presenting with a bulbous ap-pearance, is the most common manifestation of phymatous changes [151]. Similar lesions may occur in different facial locations including the ears (otophyma), forehead (meto-phyma), and chin (gnathophyma).

Physical procedures, such as surgical treatments (e.g., electrosurgery, dermabrasion, cryosurgery, and scalpel excision), and ablative laser surgery with CO_2 laser (10,600 nm) and Er:YAG (2940 nm) are often necessary to correct the shape of a deformed nose in phymatous rosacea [152–154].

Among the pharmaceutical agents, isotretinoin has been associated with better prognosis of rhinophyma and the shrinkage of the overall volume of phymata by reducing the size of the sebaceous glands. Although it does not appear to be a curative option, it could represent a good strategy after laser treatment to prevent relapse [155,156].

4.4. Ocular Symptoms

Ocular symptoms are mainly represented by chronic blepharoconjunctivitis, episcleritis, chalazion, meibomian gland dysfunction, and corneal complications [2].

Patients with ocular rosacea should be referred to an ophthalmologist if they are experiencing eye discomfort and sticky eye discharge despite frequent topical lubricant use and adequate lid hygiene, especially if they ever experienced symptoms such as reduced vision and ocular pain [75].

While general suggestions such as lifestyle changes, avoidance of triggers, ocular hygiene, and proper ocular moisturization are not sufficient in the management of ocular rosacea, topical or oral treatments are recommended. Topical cyclosporine, topical azithromycin, and topical tacrolimus currently represent the most supported therapies in ocular rosacea [157]. Moreover, a retrospective study reported that seven ocular rosacea patients treated with doxycycline 40 mg, in a slow-release form, experienced a clear improvement after an average of 2.29 months of therapy [158].

Something that is noteworthy is that the long-term use of topical corticosteroids should be avoided due to side-effects such as ocular hypertension, glaucoma, posterior subcapsular cataracts, and tear-film instability [159].

To date, novel therapeutic perspectives include intense pulsed light therapy for the treatment of evaporative dry eye disease with chronic meibomian gland dysfunction [160].

5. Conclusions

In this review, we summarize the main pathophysiological mechanisms and possible therapeutic avenues for rosacea, focusing on a phenotype-based approach. Indeed, a customized and tailored therapeutic strategy should always be pursued in rosacea, mainly based on the clinical phenotype, yet not neglecting the specific needs of each patient.

However, a more precise understanding of the molecular basis of rosacea is still needed and could hopefully lead to the identification of new therapeutic targets addressing the root cause of the disease in the near future.

Interestingly, in addition to commonly used topical and systemic therapies as well as physical approaches, new evidence is slowly emerging on the therapeutic potential of novel agents, such as monoclonal antibodies or oral small molecules (JAK inhibitors) in rosacea. Indeed, given the complex pathogenesis and the role of JAK/STAT in this disease, there is a rationale as to why JAK inhibitors could theoretically prove effective for the treatment of rosacea, as has already happened in psoriasis, atopic dermatitis, and vitiligo [161–163]. However, currently available data on the efficacy and safety of these novel therapeutic approaches are still scarce.

For all of these reasons, further clinical and translational research, as well as further clinical studies on novel or existing therapeutic agents for rosacea, should be encouraged.

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