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REVIEW

Mast Cell Stabilizers in the Treatment of Rosacea: A Review of Existing and Emerging Therapies

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ABSTRACT

Rosacea is a chronic inflammatory skin disease characterized by centrofacial erythema, papules, pustules, and telangiectasias. The onset of rosacea typically occurs after 30 years of age. It is estimated that approximately 2–5% of adults worldwide are affected. While the exact etiology of rosacea remains unknown, its pathogenesis is thought to be multifactorial with both environmental and genetic factors implicated. Ultraviolet radiation, heat, steam, ingested agents, including spicy foods and alcohol, host vasculature, dermal matrix degeneration, genetic susceptibility, and microbial organisms, including *Demodex* mites and *Heliobacter pylori*, have been implicated in the development of rosacea. Recently, mast cells (MCs) have emerged as key players in the pathogenesis of rosacea through the release of pro-inflammatory cytokines, chemokines, proteases, and antimicrobial peptides leading to cutaneous vasodilation, angiogenesis, and tissue fibrosis. Several existing and emerging topical, oral, and injectable therapeutics have been associated with improvement of rosacea symptoms based on their ability to stabilize and downregulate activated MCs. Herein, we review the data implicating MCs in the pathogenesis of rosacea and discuss interventions that may stabilize this pathway.

Keywords: Angiogenesis; Dermatologic Therapy; Emerging Treatments; Erythema; Mast Cell; Papulopustular; Rosacea

Key Summary Points

Rosacea is a chronic inflammatory skin disease characterized by centrofacial erythema,papules, pustules, and telangiectasias.

Mast cells play an integral role in the pathogenesis of rosacea via the activation andsecretion of various immune mediators.

Several existing and emerging topical, oral, and injectable therapeutics have beenassociated with improvement of rosacea symptoms based on their anti-mast cell properties.

This review may serve as a resource for clinicians and researchers exploring alternativerosacea treatments focused on mast cell stabilization.

Large-scale clinical studies are needed to determine the true efficacy of mast cell inhibitoryagents in the treatment of rosacea.

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INTRODUCTION

Rosacea is a chronic inflammatory skin disease characterized by centrofacial erythema, papules, pustules, and telangiectasias [1]. The onset of rosacea typically occurs after 30 years of age. It is estimated that approximately 2–5% of adults worldwide are affected [2–5].

While the exact etiology of rosacea remains unknown, its pathogenesis is thought to be multifactorial with both environmental and genetic factors implicated. Ultraviolet radiation, heat, steam, ingested agents, including spicy foods and alcohol, host vasculature, dermal matrix degeneration, genetic susceptibility, and microbial organisms, including *Demodex* mites and *Heliobacter Pylori*, have been implicated in the development of rosacea [6, 7]. Recently, mast cells (MCs) have emerged as key players in the pathogenesis of rosacea.

In the skin, MCs localize to the dermis in close proximity to nerve endings and blood vessels where they serve an integral role in wound healing and host inflammatory responses [8]. Following activation, MCs attract other mediators of immunity and inflammation through the release of pro-inflammatory cytokines, chemokines, proteases, and antimicrobial peptides leading to vasodilation, angiogenesis and tissue fibrosis [9, 10].

In a recent study by Aroni et al., the number and activity of MCs were found to be increased in the skin of rosacea patients as compared to control subjects [11]. Muto and colleagues expanded on this finding by demonstrating that mice lacking MCs do not develop inflammation following injection of the antimicrobial peptide, cathelicidin LL-37 (LL-37), which has been implicated in rosacea [12]; these authors also highlighted the MC stabilizer, cromolyn sodium, as a potential therapeutic in the treatment of erythematotelangiectatic rosacea [12]. In recent years, a number of topical, oral, and injectable therapeutics have been shown to alleviate the symptoms of rosacea through stabilization and inhibition of MC signaling.

In this article, we review the data implicating MCs in the pathogenesis of rosacea and discuss existing and emerging interventions that may stabilize this pathway (Table 1). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

MAST CELLS IN THE PATHOGENESIS OF ROSACEA

Mast cells are bone marrow-derived cells which circulate as immature hematopoietic progenitors and mature locally after reaching resident tissues [13]. These cells are prominent in organs that have a significant interaction with the outside environment, including the respiratory tract, gastrointestinal tract, and the skin [13]. Historically, MCs have been implicated in the pathogenesis of a number of cutaneous conditions, including atopic dermatitis, psoriasis, contact hypersensitivity reactions, autoimmune blistering disorders, and fibrosing diseases [9]. More recently, MCs have emerged as key players in rosacea via LL-37-induced skin inflammation [12, 14, 15]. LL-37 is an antimicrobial peptide synthesized and released by neutrophils, monocytes, MCs, dendritic cells, and macrophages. In addition to its function as an antimicrobial peptide, LL-37 also plays a role in angiogenesis, wound healing, immunomodulation, and immune cell recruitment. Patients with rosacea possess abnormally high levels of cathelicidin, serine proteases, and matrix metalloproteinases (MMPs) in their facial skin [14, 16, 17].

Of note, MCs are one of the primary sources of LL-37 and kallikrein 5 (KLK5), the predominant serine protease responsible for cleaving cathelicidin into its active form [16–18]. The interplay between LL-37, MCs, and the development of rosacea has been explored in animal models. Injection of LL-37 into MC-knockout mice failed to produce rosacea-like inflammation; however, when the mice were reconstituted with MCs, injection of LL-37 resulted in significant inflammation, particularly erythema, flushing, and telangiectasia formation [12]. These authors of this study also demonstrated that MC proteases and MMPs, which are

Table 1 Mast cell stabilizers in the treatment of rosacea

Modality	Treatment	Mechanism of action	Common adverse effects
Topical	Brimonidine tartrate 0.33%	Selective α2-adrenergic agonist that improves erythema via vasoconstriction; inhibits MC number and mRNA levels of MC-specific enzymes	Erythema, flushing, skin burning sensation, and contact dermatitis
	Artemether emulsion 1%	Anti-inflammatory, anti-angiogenic, and anti-MC properties	Stinging/burning, dryness, and itching
	Cromolyn sodium 4%	Inhibits MC degranulation and the subsequent release of inflammatory mediators	Local irritation, redness and burning at the site of application
Oral	Cromolyn sodium	Inhibits MC degranulation and the subsequent release of inflammatory mediators; decreases cutaneous MMP activity	Diarrhea and headaches
	Hydroxychloroquine	Suppresses MC infiltration and reducies the overall long-term survival of MCs in tissues; reduces MC expression of MMP9 and tryptase	Nausea, abdominal pain, diarrhea, pruritus, and headaches
	Artemisinin	Anti-inflammatory, anti-angiogenic, and anti-MC properties	Nausea, vomiting, anorexia, and dizziness
Injectable	Botulinum toxin	Blockage of MC degranulation by cleaving SNARE proteins within the cell	Local pain, swelling, and bruising at the site of injection

MC Mast cell, *MMP* matrix metalloproteinases, *SNARE* soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor

released from MCs upon stimulation by LL-37, are integral in promoting rosacea-like skin inflammation [12]. This eloquently designed study provides insight that LL-37 produced by MCs, and other inflammatory cells, likely results in MC degranulation leading to release of inflammatory cytokines proteases, MMPs, and onset of cutaneous rosacea symptoms. Moreover, rosacea symptoms were attenuated in wild-type mice injected with LL-37, but pre-treated with intraperitoneal injection of cromolyn sodium, a MC stabilizer [12]. Taken together, current evidence suggests that MCs play a significant role in the LL-37-induced inflammation of rosacea and that MC stabilizing agents may be a potential therapeutic target for the treatment of rosacea.

EXISTING AND EMERGING MAST CELL STABILIZERS

Cromolyn Sodium

Cromolyn sodium is one of the most recognized MC degranulation stabilizers and has been available for over 50 years, being first discovered in 1965 as a therapy for asthma [19]. In the treatment of asthma, cromolyn sodium inhibits MC degranulation and the subsequent release of inflammatory mediators, including histamine and leukotrienes, thereby preventing bronchoconstriction. It is also utilized in the treatment of allergic conjunctivitis by way of the same mechanism [20].

In the field of dermatology, oral cromolyn sodium (disodium cromoglycate; 400–800 mg/day) has been used in the treatment of gastrointestinal manifestations as well as cutaneous and neurologic symptoms associated with mastocytosis [21]. Topical cromolyn sodium 4% cream has also been utilized for the treatment of cutaneous mastocytosis, renal pruritus, and pruritus associated with atopic dermatitis [22–24]. Less studied is the effect of cromolyn sodium in the treatment of rosacea.

In a 2014 publication, Muto and colleagues demonstrated the efficacy of systemic cromolyn sodium in a cathelicidin-induced mouse model of rosacea-like inflammation [12]. In the study, intra-peritoneal cromolyn sodium was administered to wild-type mice for 4 straight days prior to LL-37 challenge. Remarkably, skin inflammation did not develop in the mice pretreated with cromolyn. Of note, MMP activity in the tissue was also dramatically decreased by cromolyn pretreatment [12].

A clinical trial investigating the use of a topical 4% cromolyn sodium ophthalmic solution in controlling facial erythema was performed in a small cohort of human subjects with papulopustular rosacea (ClinicalTrials.gov no.: NCT01933464; https://clinicaltrials.gov/ct2/show/NCT01933464). The study enrolled a total of ten patients, with five randomly assigned to be treated with cromolyn sodium solution, and the other five randomly assigned to receive normal saline placebo solution. All participants were instructed to apply their assigned solution twice daily to their face and patients returned to the clinic at 3, 6, and 8 weeks following initiation of their assigned topical solution. At 8 weeks following initiation of treatment, patients treated with 4% cromolyn sodium ophthalmic solution had a − 1.6 (standard deviation 2.6) mean change in facial erythema as compared to − 0.8 (2.8) in patients treated with normal saline placebo solution. While statistical analysis was not included, the results suggest topical 4% cromolyn sodium may be a promising treatment for facial erythema in patients with papulopustular rosacea. Of note, change in papules or pustules was not listed as an outcome measure. The aforementioned data has yet to be published. Currently, no published data assessing the use of cromolyn sodium for the treatment of rosacea exists. The common side effects of oral cromolyn sodium include diarrhea and headache. Local irritation, redness, and burning at the site of application are commonly reported adverse effects of topical cromolyn sodium.

Hydroxychloroquine

Antimalarial medications have been utilized in the treatment of dermatologic conditions dating back to the late nineteenth century when quinine was first published as an effective therapy for the treatment of lupus erythematosus [25].

Of the antimalarial drugs currently available, hydroxychloroquine (HCQ) is a well-studied medication for the treatment of cutaneous disease and has been shown to have anti-inflammatory effects. While the exact mechanism of HCQ has not been fully elucidated, it is thought to act by inhibiting ultraviolet-induced cutaneous reactions through the binding of DNA and inhibition of superoxide production [26]. Moreover, HCQ is believed to be an immunomodulatory agent, reducing the activity of inflammatory cells and decreasing the secretion of pro-inflammatory cytokines [27]. More recently, Espinosa et al. found HCQ to be an effective therapy for mastocytosis by suppressing MC infiltration and reducing the overall long-term survival of MCs in tissues [28]. These findings were translated to recent reports investigating the use of HCQ in the treatment of rosacea.

Li and colleagues investigated the role and potential mechanism of HCQ on rosacea treatment in both animal models and human subjects. The authors found HCQ reduced rosacea-like dermatitis in an LL37-induced mouse model via the attenuation of LL37-mediated MC activation, reduced MC expression of MMP9, and reduced overall expression of MC tryptase [29]. These authors also explored the effects of oral administration of HCQ 200 mg twice daily in six patients with erythematotelangiectatic and papulopustular rosacea, assessing for inflammatory lesions using the

Investigator's Global Assessment (IGA) score and for facial erythema with the Clinician's Erythema Assessment (CEA) score at weeks 0, 4, and 8. After 8 weeks of HCQ therapy, the authors observed an overall phenotypic improvement of rosacea, commenting that "the IGA and CEA scores showed a tendency to relief of rosacea." The authors also noted no obvious adverse reactions (including no discomfort of eyes) at 4 and 8 weeks post treatment. These results led the authors to conclude HCQ is a promising drug for the treatment of rosacea [29]. However, large scale clinical trials are needed to further verify the safety and effectiveness of HCQ.

A follow-up multicenter, randomized, double blind, double-dummy, pilot study performed by Wang et al. investigated the efficacy and safety of HCQ for treating rosacea. This study enrolled 66 patients with rosacea, of whom 58 (87.8%) completed the study. Patients were randomized to receive oral HCQ (200 mg twice daily) or doxycycline (100 mg once daily) and their respective placebos for 8 weeks, without any topical therapies, and were assessed at 4 visits (baseline and weeks 4, 8, and 20) [30]. Of note, baseline characteristics were similar between the two groups. At week 4, the two groups had achieved similar improvement in erythema and papules, but the noninferiority was inconclusive ($P > 0.05$). At the end of week 8, the difference in changes in total scores on the Rosacea-Specific Quality-of-Life instrument in the HCQ group was noninferior to that in the doxycycline group. The authors noted the proportion of patients with adverse events was low and similar between the HCQ (28.5%) and doxycycline (33.3%) groups. The authors highlighted the limitations of the study, which included small sample size and that for some outcomes conclusive noninferior inference could not be achieved. Overall, the authors concluded that HCQ can result in improvement of rosacea and that given the general safety profile of HCQ during pregnancy, it may be a viable option for women with rosacea [30]. While HCQ is overall well tolerated, the most common adverse effects are nausea, abdominal pain, diarrhea, pruritus, and headache. The most serious adverse effect of HCQ is dose-related retinopathy.

Artemisinin

Artemisinin (ART) is another well-studied antimalarial drug that is generally well tolerated with minimal side effects [31]. Similar to HCQ, ART has been shown to possess anti-inflammatory and anti-angiogenic properties [31, 32]. Yuan et al. explored the potential therapeutic role of ART in the well-established LL37-induced mouse model of rosacea-like dermatitis [33]. While no human subject studies were performed in their investigation, the authors found that ART ameliorated rosacea-like dermatitis by suppressing the infiltration of CD4+ T cells, neutrophils, and macrophages in mice and by inhibiting LL-37 induced activation of the NF-kB signaling pathway in human keratinocytes. The authors also demonstrated a reduction of angiogenesis in human endothelial cells treated with ART [33]. A separate study performed by Wang et al. demonstrated efficacy of a topical formulation of ART, artemether emulsion 1%, in the treatment of papulopustular rosacea in human subjects [34]. While these two studies did not investigate the role of MCs in ART-treated rosacea patients, in another study, Cheng et al. did demonstrate the anti-MC effects of ART in a mouse model of anaphylaxis [35]. When these results are taken together, it can be concluded that ART is an antimalarial agent with anti-inflammatory, anti-angiogenic, and anti-MC properties that may be an emerging therapy to treat flushing and erythema associated with rosacea. Human subjects are needed to assess for efficacy and safety in the treatment of rosacea. While ART is generally well tolerated, the common side effects include nausea, vomiting, anorexia, and dizziness. Potentially severe adverse events include prolongation of the QTc interval and cardiac arrhythmias.

Brimonidine

Topical adrenergic receptor modulators are well-established therapy for the treatment

of persistent facial erythema associated with rosacea [36]. The two α-adrenergic receptor agonists on the market are oxymetazoline 1% cream (RHOFADE cream; Allergan, Dublin, Ireland) and brimonidine tartrate 0.33% gel (MIRVASO gel; Galderma, Lausanne, Switzerland). While oxymetazoline is a selective α1a-adrenergic receptor agonist, brimonidine is a highly selective α2-adrenergic receptor agonist. Brimonidine tartrate 0.33% gel was first approved by the US Food and Drug Administration (FDA) in 2013 for the treatment of persistent, nontransient, facial erythema associated with rosacea in patients aged ≥ 18 years [36].

While numerous studies have demonstrated efficacy for topical brimonidine tartrate in the treatment of persistent facial erythema associated with rosacea, the underlying mechanisms have yet to be fully elucidated. Initial studies have shown that brimonidine acts to vasoconstrict superficial facial vessels, leading to decreased facial erythema [36, 37]. More recently, brimonidine has been linked to inhibition of MC-induced inflammation associated with rosacea [38]. In an LL-37-induced mouse model of rosacea, application of brimonidine gel significantly improved clinical erythema associated with rosacea. In mice, brimonidine gel was found to significantly decrease the number of lesional MCs and significantly reduce mRNA levels of specific MC enzymes (chymase and tryptase) increased by LL-37 [38]. While no human trials have investigated the anti-MC mechanism of brimonidine gel, data from animal studies thus far are promising. In controlled clinical trials with MIRVASO topical gel the most common adverse reactions (incidence 1%) included erythema, flushing, skin burning sensation, and contact dermatitis.

Botulinum Toxin

Botulinum toxin A (BoNT A) is a ubiquitously utilized neurotoxin in the field of dermatology. While the FDA first approved BoNT A for the treatment of adult strabismus and blepharospasm in 1989, its other therapeutic indications include spastic disorders, hyperhidrosis, migraine headaches, and facial rhytides [39]. Among its many clinical uses, BoNT A has recently emerged as a therapeutic modality in the treatment of persistent erythema and flushing associated with rosacea [40–42]. While its mechanism of action is not entirely understood, it is thought that BoNT A exerts its effects by inhibiting acetylcholine and vasoactive intestinal polypeptide release at sites of injection, thereby reducing vasodilation of superficial vessels and attenuating flushing seen in rosacea [43]. Of note, preliminary data in rats suggested a role for BoNT A in decreasing MC activity and number [44]. Subsequent studies by Ramachandran et al. demonstrated that human and mouse MCs express SNARE (soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor) proteins, including synaptosomal-associated protein-25 (SNAP-25) and vesicle-associated membrane protein (VAMP) [45].

Given recent evidence suggesting a role for MCs in the pathogenesis of rosacea, Choi and colleagues investigated the molecular mechanism by which BoNT A improves rosacea via its MC modulatory effects [46]. Through their investigations, the authors found that primary human and mouse MC degranulation is blocked by BoNT A toxin in vitro. Moreover, utilizing a mouse model of the LL-37-induced rosacea, the authors discovered that dermal MC degranulation is blocked by BoNT A toxin in vivo and that rosacea biomarkers, including chymase, KLK5, MMP9, and transient receptor potential cation channel proteins, are significantly reduced in mice treated with BoNT A [46]. The authors concluded that the mechanism of BoNT A in the treatment of rosacea involves the blockage of MC degranulation by cleaving SNARE proteins within the cell. Their data emphasize the direct inhibitory effect of BoNT A on MCs and reinforce the therapeutic role for intradermal BoNT in the treatment of rosacea. The authors also suggested a topical preparation of BoNT A may be a focus for future studies. To our knowledge, topical preparations of BoNT A have not yet been explored for the treatment of rosacea. The most common side effects of intradermal BoNT A include local pain, swelling, and bruising at the site of injection.

CONCLUSIONS

Recent data suggest that MCs play a significant role in the inflammatory pathogenesis of rosacea leading to cutaneous erythema, telangiectasias, and the formation of papules and pustules [47]. In this review, we analyzed existing and emerging MC stabilizing agents in the treatment of rosacea and explored the mechanistic roles for these agents in controlling MC-related inflammation seen in rosacea. While the evidence for MC stabilizing agents in rosacea treatment is limited, the clinical and translational data thus far is promising. Large-scale human subject studies are needed to determine the true efficacy of MC inhibitory agents in the treatment of rosacea.

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