Current and Emerging Therapies for Ocular Rosacea

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Abstract

Ocular rosacea is an incurable disease that affects millions of Americans annually. While multiple therapeutic strategies have been devised to address this disorder (including topical and oral medications, laser and light-based treatments, and surgical interventions), our current interventions are largely nonspecific and often ineffective. Nonetheless, ocular rosacea remains a source of intense research, and newer treatments offer tremendous promise for improved outcomes. In this review, we discuss the current and emerging treatment modalities for ocular rosacea and analyze novel basic science findings that will hopefully lead to highly targeted medications to treat this potentially blinding illness with greater specificity and fewer side effects.

Keywords

Ocular rosacea, ocular surface, toll-like receptor, cytokine, arteriole, intraductal meibomian gland probing, dry eye disease

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Ocular rosacea is an incurable disorder that results in significant inflammation of the eyelids and ocular surface,[1,2] and patients that suffer from this disorder are at increased risk for pain, photophobia, infection, and vision loss.[3–7] While specific estimates of the total number of patients with ocular rosacea vary considerably, over 16 million Americans are affected by acne rosacea,[8] and 58–72 % of rosacea patients develop ophthalmic findings.[9]

Despite the relatively common nature of ocular rosacea and its severe potential consequences, this disease remains difficult to treat, and disease stabilization remains elusive.

In this article, we discuss new treatment strategies for the management of ocular rosacea and outline emerging basic science findings aimed at providing targeted, highly selective therapies for this frustrating, common ailment.

Current Disease Management

Our lack of understanding of the molecular and immunologic mechanisms responsible for the onset of rosacea force us to treat patients with an array of nonspecific, less-than-optimal therapeutic strategies to minimize ocular damage. We can separate these into three main categories: the avoidance of triggers, to reduce the exposure of the ocular surface to the disease; conservative measures to minimize the damage caused by rosacea and alleviate active symptoms; and therapies to revert the damage that has already occurred.

Avoidance of Triggers

While rosacea is a persistent inflammatory condition, the ophthalmic manifestations of this disorder are often exacerbated by multiple triggers. The ingestion of alcohol, caffeine, chocolate, cheese, and specific medications have all been linked to worsening rosacea,[7] and astringent cutaneous preparations have been reported as possible pro-inflammatory agents.[10,11] Finally, prolonged sunlight exposure, extreme weather conditions, and physical and emotional stresses may all inflame the skin of patients with rosacea.[7] As such, after diagnosis, patients should be cautioned of the importance of these triggers, and should avoid them, as necessary, although the specific factors vary from patient to patient.

Conservative Measures

Given the association between ocular rosacea, meibomian gland dysfunction (MGD), and ocular surface disease,[12] patients with the cutaneous manifestations of ocular rosacea frequently develop severe blepharitis and subsequent corneal dryness and conjunctival irritation. Conventionally, the mainstay of care has been to address the manifestations of the underlying ocular rosacea with eyelid hygiene. Specifically, warm compresses are applied to the eyelids, with the intent of unclogging the meibomian glands, improving the outflow of their contents, and stabilizing the tear film. Digital massage may also be employed to liberate the meibomian gland contents, and eyelid scrubs are used to remove the crusting along the eyelids.[13]

Medical Management

Medical management with topical agents is indicated in mild cases of ocular rosacea with MGD. In order to address the ocular surface dryness inherent to ocular rosacea, artificial tears and lubricating ointments have been utilized to heal defects in the corneal epithelium. Additionally, nutritional supplementation with fish oil and flax seed has been reported to improve the symptoms of blepharitis and meibomian gland disease.[13] Furthermore, topical cyclosporine has been reported to improve ocular surface disease index scores, corneal staining patterns, and tear-production levels.[14]

More advanced cases of ocular rosacea generally necessitate oral therapeutics, although the mechanisms of action of many of these medications are unclear and often nonspecific. Several lines of evidence have demonstrated increased levels of *Demodex Folliculorum* on the skin of patients with rosacea compared with normal controls. While oral antibiotics remain the mainstay of care, considerable controversy surrounds the matter of whether the improvement in the ocular surface is due to the antimicrobial properties of these agents (i.e. decreasing pathogenic flora) or their anti-inflammatory and anti-angiogenic utilities. In either case, oral tetracycline (initiated at 500 mg, twice daily for several weeks, and then gradually decreased in a fashion that is titrated to clinical response), oral doxycycline (100 mg, once or twice daily), or a combination of a 30 mg dose of standard oral doxycycline and 10 mg of sustained-release oral doxycycline have all shown significant benefits in the treatment of this disorder.[9,12,15] Nonetheless, these medications require prolonged use and are associated with the standard risks inherent to long-term ingestion of antibiotics (including infection, multidrug resistance, gastrointestinal distress, allergy, photosensitivity, and other problems), thus raising the need for more targeted systemic therapeutics that can be tolerated for prolonged periods.

Laser and Light-based Therapies

Laser and light-based therapies have recently emerged as possible therapeutic alternatives in the management of cutaneous rosacea. Given the ability to selectively target vascular lesions, these modalities have been employed to address multiple facial lesions with excellent results. Intense pulsed light (IPL) involves the application of noncoherent wavelengths of light to affected regions of the skin, whereas laser provides a single wavelength to the skin. With either modality, the light energy is absorbed by oxyhemoglobin and converted to thermal energy, ultimately resulting in photocoagulation, thermal injury, and, ultimately, thrombosis.[16]

Papageorgiou and co-authors reported dramatic improvements in erythema, facial telangiectasias, and clinical severity after four treatments with IPL.[17] Similarly, Schroeter and colleagues documented significant, durable reductions in facial telangiectasias with the use of IPL.[18] In addition, Shim et al. demonstrated marked improvements in quality of life after treatment with pulsed dye laser.[19] Nonetheless, treatment of periocular skin was specifically excluded from these studies, making the applicability of these results to ocular rosacea somewhat difficult. Besides the obvious risk for damaging the retina using lasers or other strong sources of light, it is unclear whether this treatment would affect meibomian gland function or merely reduce the extent of the erythema without preventing corneal damage. Future investigations should explore the utility and safety of these interventions in the management of ocular rosacea.

Surgical Therapy

Surgical managements in ocular rosacea tend to focus on either enhancing the health of the ocular surface and preventing complications or interventions to address already-existing, severe, vision- and globe-threatening problems. Certainly, punctal occlusion may be employed to improve corneal dryness.[9] Originally described by Maskin, intraductal meibomian gland probing manually opens the scarred glandular orifices, thereby facilitating outflow of the contents and stabilizing the tear film.[20] A recent report documented significant enhancements in ocular surface disease scores with the use of this technique in ocular rosacea patients,[21] although the long-term consequences of this modality remain unknown.

In order to address existing complications of ocular rosacea, chalazia can be drained in the standard fashion.[9] Severe ocular surface disease that is complicated by corneal thinning may necessitate tissue adhesives, amniotic membrane transplants, and conjunctival flaps,[9] whereas penetrating or lamellar keratoplasties may be utilized to repair corneal perforations.[7]

Future Targeted Treatments—Translating Basic Science into Therapy

Currently, ocular rosacea is an incurable disease, and, despite the common nature of this disorder, our treatment options are limited and often ineffective. In fact, the aforementioned potential therapies are generally complicated by indirect mechanisms of action (i.e. the uncertain effects of antibiotics on ocular rosacea) that attempt to ameliorate the ocular surface or direct interference with already-existing tissue damage (i.e. probing to repair scarred glands, penetrating keratoplasty to address damaged corneas, etc.) Unfortunately, both variants of therapeutic interventions fail to address the inherent immunologic and molecular biologic aberrancies that ultimately result in ocular rosacea, and, instead, merely serve to mask them. However, as our knowledge of the mechanisms from which rosacea arises increases, existing medications may be employed in novel fashions and new agents may be designed to provide highly selective, targeted therapies for this disorder.

Certainly, rosacea has been associated with increased levels of cutaneous microorganisms.[22] Several investigations have explored immunologic aberrancies that may govern host responses to the stimulus of polymicrobial invasion. Specifically, Yamasaki and co-authors identified elevated levels of a family of polypeptides that are specific to leukocyte lysosomes in cutaneous biopsies of rosacea.[23] Similarly, a subsequent series of experiments demonstrated an enrichment of toll-like receptor-2 in skin biopsies of rosacea patients.[24] The toll-like receptors are a family of membrane-spanning proteins that provide surveillance against tissue damage and invading pathogens, and, upon detection, initiate and coordinate responses to clear these pathogens and/or repair the tissue.[25] Additionally, Casas and colleagues reported increased expression of genes encoding interleukin-8 and -1b, tumor necrosis factor-a, and inflammasome-related genes (NALP-3 and CASP-1)[26] in the skin of rosacea patients compared with normal controls. Selective interference or manipulation of these receptors, polypeptides, and molecules might represent novel mechanisms to reduce the pathologic inflammation associated with rosacea. Nonetheless, the ocular variant of this disease was selectively excluded from these studies, thereby complicating the applicability of these fascinating results to the management of rosacea's ophthalmic manifestations.

Several studies have focused on the inflammatory milieu of the tear film. Specifically, Barton et al. reported enrichments of interleukin-1a, normal levels of epidermal growth factor, and the absence of tumor necrosis-factor-a in the tear film of ocular rosacea patients.[27] Afonso and co-authors noted that the enriched levels of gelatinase b in the tear film of ocular rosacea patients correlated with elevations in interleukin-1.[28] These molecular abnormalities suggest that focal modulation of these proteins could be an important treatment strategy to alleviate the inflammatory changes of ocular rosacea. Ocular rosacea is, however, a cutaneous ailment with ophthalmic manifestations; the tear film is best considered a manifestation of this disease, meaning that tear-based molecular alterations may not reflect the immunologic changes that ultimately result in the clinical manifestations of ocular rosacea. Additionally, inflammation is a complex disorder that involves multiple molecules, and, to date, only a few individual mediators have been studied. In order to address these concerns, we recently explored the cutaneous molecular changes of this disease. Specifically, we assayed the concentration of 48 individual cytokines, chemokines, and vascular markers in cutaneous biopsies taken from patients with ocular rosacea and from normal controls. We identified five molecules that were enriched in ocular rosacea compared with normal controls: interleukin-1b and -16, stem cell factor, monocyte chemotactic protein-1, and the monokine induced by interferon-gamma.[29] Importantly, the observation that there were no statistically significant differences between the two groups for the overwhelming majority of the molecules that we studied suggests that rosacea induces selective changes in the affected dermis. In light of the fact that these molecules were enriched (whereas the majority remained comparable to the levels found in normal skin), biologic agents that interfere with these particular molecules might deliver selective suppression of the inflammation associated with ocular rosacea in a highly targeted fashion that provides only minimal interference with normal cutaneous immunology and function.

Despite these promising results, this investigation produced some surprising findings. While rosacea is associated with vascular hyperreactivity,[30] our investigation into the molecular biology of this disease did not demonstrate any enrichment of vascular endothelial growth factor (VEGF), arguing against an increased angiogenesis. Instead, the observed cytokine pattern identified in ocular rosacea was strongly suggestive of an innate immune response. The hallmark of this response is the aforementioned toll-like receptor, which serves to guard against infection. This aspect of immunology essentially provides surveillance against invading pathogens and/or tissue damage and, upon stimulation, ultimately results in a nonspecific response to clear invaders. We thus hypothesized that the vascular abnormalities inherent to ocular rosacea must occur through VEGF-independent mechanisms, and that it would lead to vascular activation in response to the innate immunity reaction.

As a result, we performed immunohistochemical staining for toll-like receptor-4, CD31 (a marker of all blood vessels), intercellular adhesion molecule-1 (a marker of endothelial activation), CD105 (a marker of angiogenesis and remodeling), integrin-β3 (signaling cell adhesion molecule upregulated in angiogenic vessels) in cutaneous biopsies of ocular rosacea and normal eyelids. The total number of vessels did not differ between the two groups, again suggesting that angiogenesis is not a hallmark of rosacea. We identified statistically significant enrichments of intercellular-adhesion molecule-1 and CD105 positive arterioles in the biopsies of ocular rosacea patients. Moreover, the level of toll-like receptor-4 correlated with each vascular marker in a statistically significant way.[31] Interference with these vascular proteins has emerged for therapeutic purposes in other disease states,[32–35] suggesting that already-existing medications could be employed in novel ways to address the vascular abnormalities of ocular rosacea. Similarly, modulation of toll-like receptors has been employed for other ailments,[35] and could be modified for the management of this disease.

As our knowledge of the cellular and molecular biologic mechanisms that govern the clinical manifestations of ocular rosacea expands, new therapeutic agents will optimally provide highly selective treatments for this disease with fewer side effects. Ideally, investigations into this disorder will usher in an era of interventions that treat the inherent biochemical aberrancies that ultimately lead to the effect that this disorder has on the ocular surface, as opposed to simply camouflaging them. Consequently, the large number of patients that suffer from ocular rosacea will hopefully experience relief from its potentially severe consequences. ■

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