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Review Article

Rosacea: an update on therapeutic options

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ABSTRACT

Rosacea is a common inflammatory skin disease affecting the face usually in middle-aged individuals. The disorder is associated with a lot of psychological impact on the quality of life of the affected patient. Treatment options for this skin disease range from topical treatment options to systemic agents and even lasers. This paper will review the current and some of the upcoming treatment options for this chronic skin disease.

Keywords: Rosacea, Treatment, Update

INTRODUCTION

Rosacea is a chronic, inflammatory skin disease of obscure etiology, characterized by facial erythema and telangiectasia with varying degrees of inflammatory skin lesions like papules and pustules.[1] The disease is thought to be of immune origin with an altered innate immune response being the basic incriminating factor.[2] Main precipitating events proposed for the disease include UV-light exposure, microbes like Demodex folliculorum, hormonal imbalances especially in women, emotional stress and certain systemic illnesses.[2,3] These precipitating factors are thought to mediate the changes in the dermal vasculature and cause a lymphohistiocytic infiltration in genetically susceptible individuals.

Rosacea is a disease of middle age and majority of the affected individuals belong to the 30-50 year age group.[4,5] Females are more commonly affected than males and up to about one-third of patients have a positive family history of the disease.[4,5] Morphologically, four different variants of rosacea are identified. These include the commonest erythmatotelangiectatic type, papulopustular type, ocular type and phymatous type.[5]

Treatment of rosacea is aimed at ameliorating the signs and symptoms of the disease which leads to improvement in the psychological profile of the patient. It is important to remember that rosacea can lead to a lot of negative psychological effect in the patient and this in turn can lead to aggravation of the primary disease.[6] To break this vicious cycle, an effective treatment of the primary disease is of paramount importance.[6] In addition to the therapeutic options employed in the disease, avoidance of triggering factors, UV-protection and proper skin care are equally important in the management of rosacea. Treatment options for rosacea can be divided into three main groups; topical treatments, systemic treatments and laser/light sources. All these treatment options are discussed below:

TOPICAL TREATMENTS

Topical treatment options form the mainstay of rosacea treatment and are the only intervention needed in less severe cases. Many new topical treatments have become available over the last few years and many more are currently being investigated for their therapeutic efficacy in rosacea.

AZELAIC ACID

Azelaic acid is a dicarboxylic acid mainly used in dermatology practice for the treatment of acne and epidermal pigmentation of varied causes. In addition to these two main indications, Azelaic acid is one of the primary topical agents used for the treatment of mild to moderate rosacea.[7,8] The drug is used as once daily or twice daily application in a strength of 15% to 20% in a gel or cream form. One clinical study has found once daily application of the drug to be as efficacious as twice daily application.[9] Common adverse effects encountered with the use of azelaic acid include dryness of the facial skin, burning and mild inflammation. These adverse effects usually settle down over time and discontinuation of the drug is not needed in most cases.

METRONIDAZOLE

Topical metronidazole is one of the oldest topical drugs used for the treatment of rosacea.[10] The drug has shown consistent therapeutic results in a number of clinical trials conducted over the last two decades.[11,12] The drug is available usually in a gel form and is used twice daily on the affected area. Dryness and irritation of the skin are the most common adverse effects encountered. Metronidazole has been compared with azelaic acid for therapeutic efficacy in rosacea and has been found to be as effective as the latter in clinical studies.[13,14] However, the overall effect of azelaic acid was found to be superior in these clinical trials.

TACROLIMUS

Tacrolimus has been used topically in the treatment of rosacea especially in patients with steroid abuse.[15] In one clinical study, topical tacrolimus was combined with oral tetracyclines in treatment of steroid induced rosacea with good therapeutic results.[16] Tacrolimus is supposed to help the erythematous component of rosacea rather than the popular or pustular lesions.[17] There is a report of immunosuppressive effect of tacrolimus on the proliferation of Demodex folliculorum.[18]

PIMECROLIMUS

Pimecrolimus is another calcineurin inhibitor that has shown a good therapeutic effect in rosacea patients. One clinical study on 30 patients of rosacea demonstrated a significant reduction in disease severity scores after 4-weeks of treatment with 1% pimecrolimus cream.[19] In another clinical study pimecrolimus was compared with topical metronidazole in the management of rosacea and both the treatment options were found to be equally efficacious.[20]

CLINDAMYCIN

Clindamycin is a topical antibiotic used commonly in the treatment of acne. The drug is used as an off-label medication in patients with rosacea especially those with prominent inflammatory lesions. One clinical study has demonstrated the efficacy of clindamycin-benzoyl peroxide combination in rosacea and found the combination to be as efficacious as topical metronidazole.[21]

SODIUM SULFACETAMIDE WITH SULPHUR

A combination of sodium sulfacetamide 10% with sulphur 5% is a popular old treatment for acne and seborrheic dermatitis. The combination is available as a topical lotion or a cream formulation and has shown good efficacy in rosacea treatment.[22] This combination has been compared with topical metronidazole with both the agents showing equally gratifying results in inflammatory lesion counts as well as the severity of erythema in rosacea.

MISCELLANEOUS TOPICAL TREATMENTS

In addition to the topical agents described above, there are many others which have shown anecdotal positive results in rosacea. These topical treatment options include terbenafine, permethrin 5% and topical retinoids.[23-27] In addition there are some new topical treatment options on the block which have shown a good promise in rosacea management. The most important of these is the new class of topical adrenergic blockers like Brimonidine and Oxymetazoline.[28,29] Owing to their vasoconstrictive ability, these drugs are the best bet to treat the erythema associated with the disease which is traditionally resistant to all other topical treatments used till date. Oxymetazoline has been used as a topical cream in the management of erythematotelangiectatic rosacea with excellent therapeutic results.[28] Brimonidine, which is basically used in ophthalmology as a topical anti-glaucoma drug, has also been formulated as a topical gel for the treatment of rosacea associated erythema.[29]

SYSTEMIC TREATMENTS

As a general rule systemic treatment options are used is the more severe forms of rosacea and they can be used in combination with the afore-mentioned topical treatments or even as monotherapy. Three main classes of systemic treatments are used in management of rosacea and these include antibiotics, retinoids and miscellaneous agents. Antibiotics used in rosacea are either tertacyclines or macrolides and they include doxycycline, minocycline, azithromycin and clarithromycin.

DOXYCYCLINE

Doxyclcline figures among the oldest treatments used in rosacea and despite being in used for about 4-5 decades, it is still a popular treatment option in this disease.[30] It is not clearly known how doxycycline exerts its therapeutic effect in rosacea as there is no clear-cut bacterial pathogen involved in the pathogenesis. It is believed that

doxycycline exerts anti-inflammatory effect in rosacea by way of its inhibitory effect on neutrophil migration and chemotaxis.[31] In addition doxycycline also inhibits the activation and proliferation of lymphocytes and even inhibits angiogenesis.[31]

The usual dose of doxycycline used in acne and other related disorders is 100mg once daily and the same dose can be used in rosacea as well. The drug is used for a total duration of 3 months and the dose is preferably given at bed time. Studies have also documented that a relatively smaller dose of 40mg once a day is also effective in rosacea.[32-34] Giving a lower dose of the drug obviates many of the disadvantages of giving an 'antibiotic drug' for a long duration (long-term antibiosis).[35] The incidence of Candidal vulvo-vaginitis, gastro-intestinal distress and most importantly, antibiotic resistance can be greatly minimized if such a sub-antibiosis dose is used. In fact, the first FDA approved formulation of doxycycline for rosacea is a 40mg capsule with 30mg immediate release and 10mg delayed-release doxycycline beads.[34] Two recent randomized controlled trials have demonstrated the excellent efficacy of a 16-week course of oral doxycycline 40mg once a day.[36] Oral doxycycline has also been combined with topical metronidazole with excellent results.[37]

AZITHROMYCIN

Among the macrolide group azithromycin and clarithromycin have been used in the treatment of rosacea with success. Many clinical studies have demonstrated the efficacy of oral azithromycin in the treatment of rosacea. In one clinical study there was 89% reduction in inflammatory lesion count after a 12-week course of azithromycin as a monotherapy.[38] The drug is used over a period of 12 weeks with reducing doses and is helpful in patients who are allergic or intolerant to tetracyclines.[38] Clarithromycin is another macrolide that has shown a good therapeutic effect in rosacea and is claimed to lead to a more rapid response than oral doxycycline.[39,40]

ISOTRETINOIN

Isotretinoin is claimed to help all the pathophysiological stages of rosacea but the exact mechanism of action of this drug remains to be unclear. There are some clinical studies in the world literature that have shown a significant benefit in patients with rosacea with isotertinoin treatment.[41] One of these studies have demonstrated the effectiveness of a low dose isotertinoin treatment in the dose of 10 mg/day for 4 months in therapy-resistant rosacea.[42]

ORAL METRONIDAZOLE

Metronidazole is given in a dose of 200mg twice daily in the treatment of rosacea.[43] A 6-week course of oral metronidazole leads to a significant reduction in all the inflammatory lesions of rosacea.[43] The drug has been compared with oxytetracycline in the treatment of rosacea with almost equivalent therapeutic effect with both these drugs.[44] The adverse effect profile of this drug needs to be kept in consideration while prescribing it in rosacea as the treatment duration is not in days but in weeks.

ORAL ZINC SULPHATE

A randomized cross-over trial in 25 patients demonstrated the therapeutic effect of oral zinc sulphate in rosacea.[45] The drug was given over 3 months and lead to a significant reduction in the severity of rosacea in treated patients.[45] On crossing over to the placebo group, the severity score increased once again but remained lower than the baseline values.

LASERS AND LIGHT SOURCES

Lasers and light sources that target cutaneous blood vessels have been tried in rosacea including therapy-resistant rosacea. Vascular lasers and light sources are possibly effective in rosacea because of two reasons; firstly, the basic pathogenic mechanism in rosacea is thought to be vasomotor instability and secondly, telangiectasia and increased vascularity of the face are invariably seen in the disease. In fact, light-based treatments have revolutionized the treatment of rosacea over the last two decades as they help in the resolution of not only the inflammatory component but also in the erythematous or telangiectatic component as well.[46,47]

Among the light-based sources, Intense Pulse Light (IPL) is the one most commonly reported to be useful in rosacea.[47,48] In a study on 34 patients the mean erythema score improved by 39% and the telangiectasia by 55% after 4 treatment sessions with IPL at 3-weekly intervals.[49] Moreover, the results obtained were sustained at 6-months and the side effects were really negligible. In another study with a long-term follow up, 60 patients with rosacea associated telangiectasia were treated with an average of about 4 sessions with IPL and the mean clearance rate achieved was 77.8%. Significantly, the clearance was maintained over a mean follow-up period of 51.6 months (range of 12 to 99 months).[50]

Another light-based device used in the treatment of rosacea is the pulsed dye laser (PDL).[51] The therapeutic effect of this laser in rosacea was compared with IPL in one split-face randomized controlled trial on 29 patients.[51] Three sessions were performed with the two machines at monthly intervals and the results were evaluated by spectrophotometric methods. Both the systems were seen to lead to significant reduction in severity scores and the therapeutic efficacy as well as adverse-effect profile was similar with both.[51]

CONCLUSION

Rosacea continues to be an elusive skin disease with no well-defined etiopathogenesis. Many new treatments

have been discovered over the past two decades for this disease but the age-old treatments like metronidazole and oral doxycycline still hold their fort

Treatment of a patient with rosacea depends upon the severity of the disease and its psychosocial impact. While patients with a less severe disease can be managed with topical treatments like azelaic acid, metronidazole or calcineurin inhibitors, the more severe variants need some systemic treatment. On the systemic front, oral doxycycline and macrolides are the most commonly used drugs which are useful in tackling especially the inflammatory component of the disease. Light-based treatments especially with IPL or PDL have shown a lot of promise in treating rosacea and they seem to be particularly useful in the management of vascular component of the disease.

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