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THERAPEUTIC RESPONSE OF ROSACEA TO DOBESILATE

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Abstract: Despite an incomplete understanding of the pathogenesis of rosacea, therapeutic modalities continue to expand. The principal subtype of rosacea includes erythematotelangiestatic rosacea, which is characterized by uncontrolled angiogenesis. Angiogenic growth factors such as fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) are currently targets of intense effort to inhibit deregulated blood vessel formation in diseases such as cancer. Here we report a 33-years-old woman with erythematotelangestatic rosacea who responds to a daily treatment of topically applied dobesilate, an inhibitor of FGF, with an improvement in erythema and telangectasia after two weeks. Thus, dobesilate might be useful in the treatment of rosacea and other diseases that depend on pathologic angiogenesis.

Key words: Rosacea, Topical therapy, Dobesilate.

INTRODUCTION

Rosacea is a common cutaneous disorder that predominantly affects fair-skinned Caucasian people, although all races may be affected. Clinical manifestations of rosacea are primarily distributed on the central convexities of the face, including the cheecks, chin, nose and forehead. The primary features include nontransient erythema, flushing and telangectasia [1]. Rosacea may significantly affect patient's mood, leading to considerable emotional distress and withdrawal from social interactions. Thus, there is a need for new agents because no medication has proven to be beneficial for this skin disease.

Angiogenesis is the outgrowth of new blood vessels from existing ones. It occurs during development, but usually stops in maturity. In healthy adults it only appears in the endometrium and ovaries during menstrual cycle, and in conditions associated with tissue repair and inflammation [2]. However, prolonged and excessive angiogenesis has been implicated in different pathologic processes as rheumatoid arthritis, psoriasis, rosacea, keloids, contact dermatitis, obesity, endometriosis, diabetic retinopathy, restenosis, atherosclerosis, tumor growth and metastasis, and revascularization of ischemic myocardium, hind limb muscles and brain [3-9]. Blood vessel formation in the body is strongly up or down regulated by a number of factors. The tyrosine kinase receptor ligands, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) are examples of extensively studied stimulators of angiogenesis [10, 11]. The positive signals for blood vessel formation are opposed by natural and synthetic antiangiogenic agents [12].

Although the pathogenesis of rosacea is unknown, there is strong evidence for the involvement of angiogenesis [13-17]. Because FGF and VEGF participate in several steps of the pathogenic pathways of angiogenesis-dependent skin diseases [18, 19], they are main targets for drug development in treatment and/or prevention. Calcium dobesilate (Doxium®), which has been widely used for the treatment of diabetic retinopathy [20], has been reported to act as a synthetic inhibitor of FGF [21]. Based on this finding, we assessed the effect of dobesilate in rosacea.

CASE REPORT

A 33-years-old woman presented with erythematotelangectatic rosacea. Patient gave written informed consent before starting study. The face was treated with calcium dobesilate (2.5 percent in a suspension formulation), applied twice daily by the patient herself for a maximal period of two weeks. Ointment consists of 2.5% calcium dobesilate on a weight/weight basis, compounded with propylene glycol, polyethylene glycol 600 distearate, hydroxypropyl cellulose and purified water. Photographs were taken before and after study completion. Compliance was judjed to be good because of the patient's high motivation. As Figure 1 shows, topical dobesilate led to a significant improvement in erythema and telangectasia. Furthermore, the symptoms of flushing, burning and stinging sensations were all reduced after treatment, with no recurrence four months after stopping the therapy.

DISCUSSION

Angiogenic factors, such as FGF and VEGF, stimulate endothelial cells to release several proteases and plasminogen activators, resulting in degradation of the vessel basement membrane, allowing cells to invade the surrounding matrix. The cells migrate, proliferate and eventually differentiate to form a new lumen-containing vessel. Finally, the endothelial cells make up a new basement membrane and secrete growth factors, such as platelet-derived growth factor (PDGF), which attracts supporting cells such as pericytes that ensure the stability of the new vessel [22]. FGF has been reported to be a potent inducer of VEGF in various cell types [23-28].

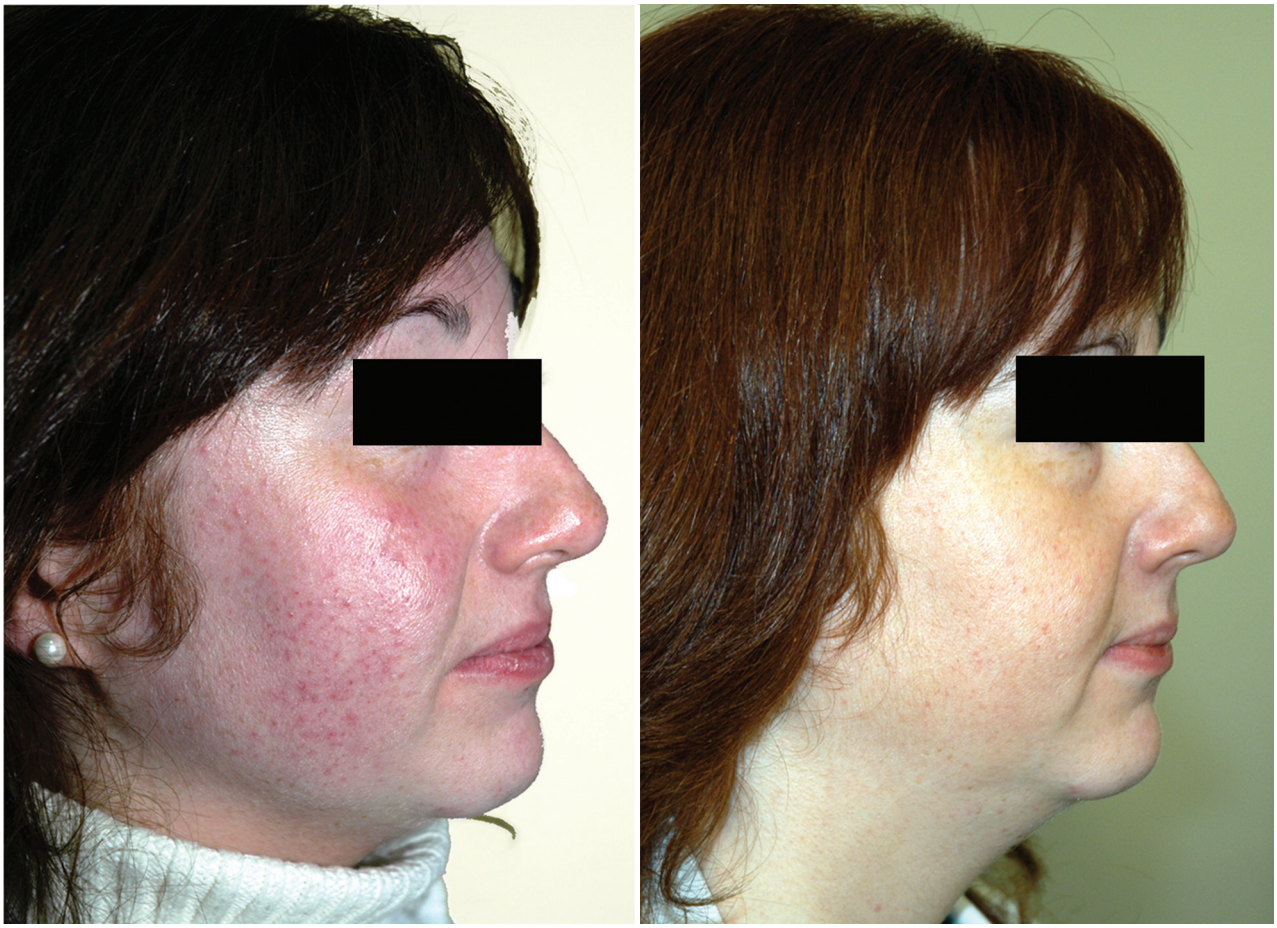

Fig. 1. Patient before (left) and after (right) treatment with dobesilate during two weeks. Note improvement in background erythema and telangectasia.

In addition, FGF acts synergically with VEGF in the induction of angiogenesis probably by upregulating VEGF and VEGF receptors in endothelial cells [29-31]. Recently it has been reported that FGF, together with VEGF, contributes to tumor angiogenesis and that inhibition of their activities halts tumor growth [32]. Thus, therapeutic approaches based on the inhibition of FGF function may allow the simultaneous targeting of different cell types. Moreover, such treatment may potentiate the inhibition of VEGF function in cases in which both factors are expressed and act in a synergistic manner.

Local inhibition of angiogenic factors function by dobesilate may prevent skin angiogenesis and inflammation in rosacea and other angiogenesis-dependent skin diseases in which a dense network of new vessels is produced and inflammatory cells are present. This molecule may also play a role in the reduction of inflammation [33] by regulating the synthesis of inflammatory molecules in rosacea. Furthermore, since FGF acts as survival factor for many cell types including endothelial cells [34, 35], it is likely that inhibiting FGF function by dobesilate [21] represents a biological relevant mean of producing apoptotic endothelium in rosacea vessels. This case report demonstrates the efficient and safe benefits of dobesilate suspension 2.5% in the treatment of rosacea, providing a new and attractive therapeutic option for the treatment of this disease.

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