A Retrospective Case Series Review of the Peroxisome Proliferator-Activated Receptor Ligand Rosiglitazone in the Treatment of Atopic Dermatitis

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Background: Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that are expressed in a variety of cells, including keratinocytes and cells of the immune system. The γ subtype, activated by the antidiabetic thiazolidinediones, was originally identified as a regulator of adipogenesis and glucose homeostasis. Recent data, however, have linked PPAR-γ to several genes involved in inflammation. Among others, these pathways reduce certain inflammatory mediators in the skin and regulate epidermal barrier homeostasis, alterations of which contribute to the inflammation associated with atopic dermatitis (AD). To our knowledge, the addition of rosiglitazone maleate to the standard treatment of AD has not been evaluated.

Observations: Severe adverse events were not observed, although 1 patient experienced weight gain. All patients responded to rosiglitazone therapy with decreased total body surface area involvement, severity of lesions, and number of flares.

Conclusions: Rosiglitazone, a drug that has an excellent safety profile, may offer a well tolerated systemic treatment option for AD. However, its role should be further assessed in controlled trials to establish its efficacy and safety in this disease.

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A TOPIC DERMATITIS (AD) is a common inflammatory skin disease with a lifetime prevalence of 10% to 20% in children and 1% to 3% in adults. The disease displays a relapsing course that can lead to considerable morbidity, social isolation, and emotional stress. Although the exact etiology of AD is not clear, cutaneous hyperresponsiveness to environmental stimuli, epidermal barrier dysfunction, and genetic susceptibility are all believed to play an important role. Atopic dermatitis is thought to result from a complicated interaction between altered keratinocytes, activated T cells, mast cells, and dendritic cells, their products, susceptibility genes, and the host environment. However, T cells dominate the cellular infiltrate, and drug agents that interfere with T-cell activation, including the calcineurin phosphatase inhibitors cyclosporine, topical tacrolimus, and pimecrolimus, result in improvement of clinical disease. Acute lesions of AD reflect a T helper cell type 2 (TH2) mediated response with up-regulation of interleukin 4 (IL-4), IL-5, and IL-13. These cytokines contribute to the high levels of IgE and eosinophilia that characterize this disease. This is in contrast to T helper cell type 1 (TH1) responses, which are characterized by high levels of interferon gamma and IL-2. If acute skin lesions progress to chronic disease, however, the initial TH2 response evolves to a mixed TH2/TH1 picture. As a result, the infiltrate changes to include additional antigen-presenting cells, macrophages, and eosinophils, with fewer T cells.

The factors responsible for the polarization toward TH2 activation in individuals with AD is uncertain. Recently, there has been increased attention on the epidermis as the primary defect in AD. Defective permeability barrier function enables the enhanced penetration of environmental allergens and induces a cytokine milieu favoring a TH2 response. In support of this view, 2 common loss-of-function mutations in the filaggrin gene, which is situated on the epidermal differentiation complex chromosome 1q21, have been identified as major predisposing factors for AD. Besides structural abnor-

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malities, keratinocytes of patients with AD also display an intrinsic defect in cytokine production. Because the local cytokine milieu affects dendritic cell maturation and activation, this has implications in AD. In particular, keratinocyte overexpression of thymic stromal lymphopoietin, an IL-7-like cytokine, in lesional AD skin enhances T<sub>H</sub>2 responses by inducing the migration of dendritic cells into the lymph nodes. These findings shed new light on the role played by epithelial cells in allergic inflammation.

Treatments for AD are aimed at controlling inflammation with emollients, topical corticosteroids, and topical immune modulators, such as topical tacrolimus and pimecrolimus. For patients with disease that does not respond to topical therapy, UV light (both UV-B and UV-A with or without 8-methoxypsoralen) can be useful. For patients with the worst disease, systemic corticosteroids are occasionally used to manage acute flares, and immunosuppressives, such as cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and biologic drugs have been reported. Many patients with AD, however, cannot tolerate or do not respond to standard treatments and are averse to the risks of immunosuppressive agents; thus, new options are needed. Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists play a critical role in the regulation of genes that are involved in cellular proliferation, specific components of the T<sub>H</sub>2 inflammatory pathway, and maintenance of the skin barrier. They are also involved in the regulation of lipid metabolism. All of these factors seem to be important in the pathogenesis of AD.

Rosiglitazone maleate, a thiazolidinedione, is a PPAR-γ agonist that is approved for the treatment of type II diabetes mellitus. Because rosiglitazone is a well tolerated medication with an established safety profile, we examined patients with severe AD who were either resistant to or unable to tolerate their treatment regimen and who received rosiglitazone as an addition to their therapy.

### REPORT OF CASES

#### CASE 1

Since childhood, a 16-year-old girl had had allergic rhinitis and AD that was resistant to intensive topical steroids, topical tacrolimus, and cetirizine hydrochloride. Stress, extremes of temperature, certain foods, grass, pollen, dust, and animals resulted in flares of AD. A physical examination demonstrated xerosis with scaling, erythematosus, hyperkeratotic, and lichenified plaques involving 70% of her total body surface area (TBSA). Rosiglitazone maleate, 2 mg twice daily, and hydroxyzine hydrochloride, 25 mg at bedtime, were added to her previous regimen of topical steroids and topical tacrolimus. The patient returned 1 month later with involvement reduced to 5% TBSA. The acute eczematous lesions resolved, leaving her with minimal xerosis and hyperpigmentation. Once the flare resolved, rosiglitazone was discontinued after 4 months of therapy. No adverse effects were seen with rosiglitazone. Topical steroids were tapered to every other day, and topical tacrolimus was continued. To date, after 8 months, the patient remains in remission with no new flares.

#### CASE 2

A 17-year-old girl with asthma and hay fever presented with severe AD, which she had had since early childhood. Despite treatment with antihistamines, intensive topical fluorinated corticosteroids and emollients, antibiotics, and topical tacrolimus, the patient had severe and active disease with erythema, exudation, and erosions affecting 80% of her TBSA. Similar flares occurred 3 times per year. Rosiglitazone and total-body occlusive wraps with fluticasone propionate were added to the patient’s regimen. One week later, involvement was reduced to 10% TBSA. The exudation was no longer present, and the erythema was less pronounced. With resolution of the flare, rosiglitazone therapy was discontinued and topical steroids were tapered. The patient returned 1 month later with a severe flare involving 70% of her TBSA. The exacerbation was most likely precipitated by a very rapid systemic steroid taper for an asthma flare. She was treated with rosiglitazone maleate, 4 mg twice daily; hydroxyzine; a 10-day course of cefadroxil; triamcinolone acetonide for 5 d/wk; and fluticasone propionate under occlusion for 2 d/wk. Within 3 months, involvement was decreased to 5% TBSA, and topical steroids were tapered while rosiglitazone was continued. The patient did not experience new flares during 12 months of follow-up. No adverse effects were seen with rosiglitazone, and to date the patient continues to receive rosiglitazone.

#### CASE 3

A 37-year-old man presented with a history of allergic rhinitis and a 15-year history of recalcitrant AD that had been previously treated with repeated intramuscular triamcinolone acetonide and a Chinese herbal tea. Stress and numerous food allergies, which were confirmed by allergen testing and treated with weekly allergy shots, exacerbated his condition. A physical examination revealed diffuse erythema, exudation, and excoriations involving 90% of his TBSA complicated by perioral pyoderma with severe facial disfigurement from erythema and periorcular edema, atopic keratoconjunctivitis, keratoconus, and blepharitis. His treatment regimen consisted of intramuscular steroids, antihistamines, oral antibiotics, and topical steroids. The patient was treated with cyclosporine, 3.5 mg/kg/d for 1 month, and he improved to 30% TBSA involvement. The cyclosporine was tapered to 3.0 mg/kg/d and supplemented with psoralen and UV-A therapy, fluticasone propionate cream, and topical tacrolimus ointment. After being prescribed cyclosporine for 11 months, despite involvement reduced to 20% TBSA, resolution of the acute inflammatory changes, and only 2 flares of disease, the cyclosporine had to be discontinued owing to renal toxic effects, and rosiglitazone maleate, 2 mg twice daily, was added as an alternative. After 1 month, involvement was maintained at 20% of his TBSA. The dosage of rosiglitazone maleate was subsequently increased to 4 mg twice daily after 3 months. Following 2 years of treatment at this dosage, skin in-
volvement was reduced to 5% TBSA, and the frequency of exacerbations was further improved to 1 flare per year despite the substantial reduction in the use of topical steroids and immunomodulators and the cessation of intramuscular steroids. However, he experienced a 7-kg weight gain. Although lack of fluid retention in the lungs and the skin made rosiglitazone therapy an unlikely etiology, the rosiglitazone maleate dosage was reduced to 3 mg twice daily for 1 month and then to 2 mg twice daily thereafter. After 8 months, the patient’s AD remained well controlled at 10% TBSA involvement without further weight gain or weight loss.

CASE 4

A 75-year-old woman with AD during childhood and detergent contact dermatitis during adulthood presented with a 2-month history of a recalcitrant AD. Her AD recurred at age 70 years and steadily worsened until presentation. Her daily treatment regimen consisted of prednisone, 30 mg, hydroxyzine hydrochloride, antihistamines, and emollients. Although stress was her main trigger, a drug reaction to antibiotics precipitated her most recent flare. A physical examination demonstrated poorly controlled severe and chronic skin lesions involving 35% of her TBSA. Oral steroids were tapered, and topical tacrolimus and topical steroids were added to her previous regimen. Numerous attempts to lower the steroid dosage to less than 10 mg/d resulted in 4 severe flares that were unresponsive to UV-B therapy, superpotent topical steroids, and antibiotics. A 4-week course of prednisone, 25 mg/d, cleared her skin to 10% TBSA involvement. At that time, rosiglitazone maleate, 2 mg twice daily, was added to her usual treatment. At her 3-month follow-up, she returned with 2% TBSA affected. Her prednisone was successfully tapered to 2.5 mg every other day, and topical tacrolimus was decreased to every other day. After 1 year of clinical stability on this regimen, she had a flare of her disease, and rosiglitazone therapy was discontinued.

CASE 5

A 40-year-old man presented with a 10-year history of severe adult-onset AD. Despite treatment with numerous antihistamines, topical steroids, topical tacrolimus, oral and topical antibiotics, psoralen–UV-A, methotrexate, cyclosporine, and mycophenolate mofetil, he continued to have baseline severe disease with at least 2 exacerbations per year. Notable improvement only occurred with a combination of antibiotics and high-dose topical steroids, which resulted in Cushing syndrome. At presentation, his regimen consisted of mycophenolate mofetil, topical tacrolimus, cetirizine, and montelukast sodium. A physical examination revealed erythematous, exudative, excoriated, and lichenified plaques involving 75% of his TBSA. Treatment with a prednisone taper, fluticasone propionate ointment (applied twice daily every day for 2 weeks, followed by twice daily application every other day for 2 weeks, followed by twice daily application on 2 consecutive days, followed by 5 days off treatment every week thereafter), topical tacrolimus, and doxepin hydrochloride was started. Despite intensive treatment, the patient returned 11 months later with similar lesions involving 90% of his TBSA. Rosiglitazone, a slow prednisone taper, triamcinolone acetone, fluticasone propionate as needed, and pimecrolimus were added. Rosiglitazone maleate was started at 2 mg twice daily for 2 weeks and then increased to 4 mg twice daily. After 4 months of treatment, despite the completion of the steroid taper 4 weeks earlier, the patient improved to 75% TBSA involvement. There was resolution of acute changes with residual lichenification and mild erythema. No adverse drug effects were seen with rosiglitazone, and to date there have been no relapses of AD during 12 months of follow-up.

CASE 6

A 69-year-old man presented with a 20-year history of severe adult-onset AD. Previous treatments, which included emollients, atopiclair, topical steroids, topical tacrolimus, pimecrolimus, and interferon gamma, provided only temporary relief. On presentation, he had erythematous, exudative plaques involving 60% of his TBSA. His regimen consisted of emollients, halobetasol propionate cream, topical tacrolimus, and pimecrolimus. Rosiglitazone maleate, 2 mg twice daily, and a 1-month course of cephalexin were added to his regimen. Two months later, the dosage of rosiglitazone maleate was increased to 4 mg twice daily. After 5 months of treatment with rosiglitazone, the patient improved to 20% TBSA involvement with decreased infiltration and exudation. The patient did not experience any new flare during the 9 months of follow-up. No adverse drug effects were seen with rosiglitazone, and to date the patient continues to receive rosiglitazone.

COMMENT

In this retrospective review of 6 patients, rosiglitazone treatment addition was associated with increased control of severe AD that was not responsive to first- and second-line therapies. All 6 patients, who ranged in age from 16 to 75 years, showed decreased extent of the disease, inflammation, and number of flares. In addition, rosiglitazone allowed the gradual reduction or elimination of systemic steroids in the 3 patients who used them. Major clinical improvement appeared between week 4 and week 12, suggesting that some patients may require at least 3 months for a clinical response. Because the management of AD is complicated by the fluctuations in severity, there is uncertainty as to whether improvements are attributable to treatment or to the natural course of disease. However, because our patients experienced a decreased number of flares compared with baseline, it seems that rosiglitazone affected the natural course of the disease. Furthermore, once a response was achieved, 4 patients maintained clinical stability for at least 12 months of treatment. The decrease in flares and, thus, the need for rescue treatment with topical and oral steroids suggests that rosiglitazone may be able to act as a steroid-sparing maintenance agent in severe disease. These findings occurred in the setting of excellent tolerability.
Adverse events seen with rosiglitazone include dosage-dependent weight gain, which is most likely due to fluid retention and fat accumulation. The incidence of pedal edema ranges from 3% to 5%, and there is an increase in plasma volume, which is likely to be responsible for the mild reduction in hemoglobin level seen with thiazolidinediones. Because rosiglitazone can cause fluid retention, this drug may pose a cardiovascular risk. A recent meta-analysis of data from 42 clinical trials found a 43% increase in relative risk of myocardial infarction among patients with type 2 diabetes mellitus treated with rosiglitazone. Although the clinical significance of these findings must be confirmed, this study raises concern about the use of rosiglitazone in patients with cardiac risk factors. Therefore, susceptible patients should be closely monitored for myocardial infarction and worsening cardiac function. In addition to fluid retention, the weight gain may also be caused by increased adipogenesis with a reduction in waist-hip ratio. This suggests a shift in fat distribution from visceral to subcutaneous fat, conferring less cardiac risk. Although available clinical data show no evidence of rosiglitazone-induced hepatotoxicity or alanine aminotransferase elevations, rosiglitazone has a common thiazolidinedione structure that is very similar to troglitazone, which has been associated with severe idiosyncratic hepatotoxicity that resulted in its loss of US Food and Drug Administration approval. For these reasons, it is recommended that liver function tests be obtained before initiating therapy with rosiglitazone and periodically thereafter. Although most experience with rosiglitazone is in adults, a recent large-scale trial in children and adolescents with diabetes mellitus points to a good safety profile for rosiglitazone in pediatric populations. In patients receiving rosiglitazone (age range, 8-17 years; n=99), there was 1 event of mild peripheral edema and a mean weight gain of 3 kg at the end of the study vs no weight gain among patients treated with metformin.

Adverse effects of rosiglitazone were monitored by assessing laboratory values, patient weight, and volume status. Complete blood cell counts and liver enzyme levels were monitored, but none of the patients showed dilutional anemia or abnormal liver enzyme levels during therapy. One patient gained 7 kg. Although there were no signs of fluid overload on physical examination, and weight gain occurred 1 year after the onset of treatment, it is not possible to exclude rosiglitazone as a cause of this weight gain.

Even though the efficacy of rosiglitazone in AD cannot be concluded from these results, PPAR-γ agonists may limit the cutaneous inflammation and immune response seen in AD through a number of mechanisms. Peroxisome proliferator-activated receptor gamma agonists have been found in a variety of immune cells, and numerous in vitro and in vivo studies have demonstrated that this nuclear receptor modulates the transcription of cytokines and costimulatory molecules. First, it may limit T-cell activation by dendritic cells. The PPAR-γ ligands inhibit chemokine EB1 ligand and CCR7, both of which are important in dendritic cell migration to lymph nodes. The inhibition of tumor necrosis factor α–induced departure of dendritic cells from the epidermis may also play a role. Peroxisome proliferator-activated receptor gamma agonists also inhibit the production of IL-4 and IL-6 by monocyte-dependent mechanisms. This reduces IgE class switching in B lymphocytes and limits allergic response. The PPAR-γ agonists induce a dosage-dependent inhibition of IL-5, which has implications for regulating eosinophil chemotaxis. Furthermore, PPAR-γ agonists have been shown to inhibit IL-21 and IL-12, which are both important Tp1 driving factors. The reduction of both Tp1 and Tp2 cytokines may explain the improvements seen in both acute and chronic disease. These findings suggest that treatment with rosiglitazone down-regulates peripheral immune response.

The hyperactive immune response seen in AD is exacerbated by impaired skin barrier function. Disturbed lipid content, increased epidermal proliferation, and changes in epidermal differentiation have been found in AD. Recent studies have demonstrated that PPAR activators accelerate permeability barrier recovery following acute barrier disruption. Both in cultured human keratinocytes treated with PPAR activators and following topical applications of PPAR activators to normal mouse skin, loricrin, filaggrin, involucrin, and transglutaminase 1 expression increase. In patients with inflammatory cicatricial alopecia, a peroxisome defect seems to lead to alteration of lipids metabolized by peroxisomes; thus, stimulation of peroxisomes and their lipid metabolism may play a role in AD inflammation. In addition, PPAR agonists increase epidermal lipid synthesis, lamellar body secretion, and extracellular lipid processing in hairless mice. Together, these studies suggest that PPAR agonists may improve AD by remodeling the reduced lipid content and restoring skin barrier function.

Because severe AD is often treated with systemic therapies that carry considerable adverse effects, there is a great need for safer therapies. Rosiglitazone has a favorable adverse effect profile that does not include the numerous local or systemic effects of steroids and immunosuppressive agents. Peroxisome proliferator-activated receptor gamma agonists have been used in other chronic inflammatory conditions, including psoriasis, ulcerative colitis, and atherosclerosis. Specifically, in psoriasis, there are a number of case reports describing the benefit of PPAR-γ agonists. However, when rosiglitazone's efficacy in psoriasis was evaluated in 2 large-scale, randomized double-blind, multicenter studies, it failed to demonstrate any notable efficacy when compared with placebo. These observations emphasize the need for caution in interpreting the promising results of the present study. Our preliminary data suggest that patients with severe AD may also benefit from PPAR-γ agonists, whereas our findings are limited by other factors that further highlight the uncertainty of our clinical observations. The data are derived from a small number of patients in an uncontrolled, retrospective analysis. In addition, dosage regimens and length of treatment with rosiglitazone varied among patients. Adjunctive treatments were not standardized, making it difficult to know whether rosiglitazone was responsible for the clinical improvement. Despite these limitations, the 6 cases described herein suggest the possibility that rosiglitazone ameliorated the intensity of disease and allowed tapering of other systemic and topical agents to safer levels in 6 patients who had had...
many years of severe, drug-resistant AD. As a result, rosiglitazone may serve as a good alternative to current systemic immunosuppressants used for severe AD. The potential role of rosiglitazone in the treatment of AD is therefore worth evaluating in future controlled trials.

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