

CASE REPORT

Severe atopic dermatitis treated with everolimus

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Abstract

Background: Patients with severe atopic dermatitis (AD) often require treatment with oral immunosuppressive drugs. Everolimus is a rapamycin-derived macrolide with immunosuppressive and antiproliferative effects. Everolimus demonstrated efficacy not only in the prophylaxis of organ rejection in kidney transplant patients, but also in decreasing disease activity in psoriasis patients. **Objective:** To evaluate whether everolimus is an effective treatment in patients with severe AD. **Methods:** Two patients with severe AD were treated with everolimus in combination with low-dose cyclosporin A (CsA) or prednisone. During treatment, a disease activity and safety laboratory examination was performed. **Results:** Everolimus either in combination with prednisone or with CsA did not result in improvement of disease activity in two patients with severe AD. **Conclusion:** Everolimus does not seem to be an effective treatment in these two AD patients, either in combination with prednisone or with CsA.

Key words: *Atopic dermatitis, everolimus*

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease (1,2). Treatment of AD is focused on downregulation of inflammation in the skin with topical corticosteroids or topical immune modulators. Patients with severe AD require treatment with oral immunosuppressive drugs, of which the calcineurin-inhibitor cyclosporin A (CsA) has proven clinical efficacy and safety on short- and long-term treatment (3–5). Everolimus (Certican®; Novartis, Basel, Switzerland) is an immunosuppressive and antiproliferative macrolide derived from rapamycin (sirolimus). It shows increased oral bioavailability compared to sirolimus, but the mechanism of action is the same.

The effect of everolimus on T cells is different from that of CsA. CsA inhibits the mechanism leading to the synthesis of IL-2 (arresting the cell in the G0/G1 phase), whereas everolimus blocks the synthesis of the IL-2 receptor induced by IL-2 and IL-15; it inhibits, therefore, cell-cycle progression from the G1 into the S phase.

Since everolimus and CsA inhibit adjacent steps in T-cell activation, a combination of these drugs results

in a synergistic immunosuppressive activity, allowing CsA dose reduction (6,7). Sirolimus in combination with low-dose CsA is effective in the treatment of psoriasis, also a T-cell mediated disease (8). Everolimus (1.5 mg twice daily) in combination with CsA (1 mg kg⁻¹) was effective in one patient with psoriasis (9).

We describe two patients with severe AD who were treated with everolimus, one in combination with prednisone and one in combination with CsA.

Case reports

Case 1: everolimus in combination with prednisone

A 51-year-old woman with severe AD had to discontinue CsA due to therapy-resistant hypertension. Treatment with prednisone 30 mg daily induced only a moderate response. At this time she presented with active disease with a modified-SCORAD index (10) of 29 and an involved body surface of 40%. For that reason treatment with everolimus 0.75 mg twice daily was combined with prednisone 20 mg daily. Every 2 weeks a full blood count, hepatic and renal

function, cholesterol and blood levels of everolimus were measured.

After 2 weeks, the blood everolimus level was $1.3 \mu\text{g l}^{-1}$; this is below the transplantation reference therapeutic range of $3\text{--}8 \mu\text{g l}^{-1}$. For that reason the dosage of everolimus was doubled and prednisone was tapered to 10 mg daily within 2 weeks. In the following 10 weeks her eczema remained active, despite a temporary dose increase of prednisone to 30 mg daily for 7 days in week 6 when the modified-SCORAD index was 45.5 and the involved body surface was 63%. Everolimus blood levels continued to be low. Laboratory tests during treatment showed a slight decrease in haemoglobin ($7.9\text{--}7.4 \text{ mmol l}^{-1}$ after 12 weeks), which returned to baseline values after discontinuation of everolimus. Also, a transient lymphocytopenia (1.62 to $0.78 \times 10^9 \text{ l}^{-1}$) was observed after 6 weeks, which normalized after 10 weeks. Other laboratory tests were within normal limits. The patient reported no side effects. Everolimus was discontinued after 12 weeks because of lack of clinical response.

Case 2: everolimus in combination with CsA

A 62-year-old woman with severe AD was initially treated with CsA 5 mg kg^{-1} with a good clinical response; however, the dosage had to be tapered because of hypertension.

At that moment she presented with mild disease activity, a modified-SCORAD index of 9 and an involved body surface of 10%. The CsA dosage was decreased to 3 mg kg^{-1} in combination with everolimus $0.75 \text{ mg twice daily}$ to prevent an exacerbation. Laboratory tests were done every 2 weeks as previously described.

In spite of having a serum everolimus level within the therapeutic range ($3.1 \mu\text{g l}^{-1}$), her eczema exacerbated after 2 weeks with a modified-SCORAD index of 39 and an involved body surface of 39%. The dosage of everolimus was doubled to $1.5 \text{ mg twice daily}$. However, her eczema did not improve and everolimus was stopped after 9 weeks. Laboratory tests showed a decrease in haemoglobin (8.6 to 7.6 mmol l^{-1} after 9 weeks), which returned to baseline values after discontinuation of everolimus. A transient leucopenia (8.2 to $3.7 \times 10^9 \text{ l}^{-1}$) was observed after 6 weeks, which normalized after 9 weeks. Other laboratory tests were within normal limits. The patient reported no adverse effects.

Discussion

Treatment with everolimus either in combination with prednisone or with CsA did not result in improvement of disease activity in two patients with

severe AD. Patient 1 had blood everolimus levels below the therapeutic range, despite a dosage of 3.0 mg daily . This may be explained by poor therapy adherence which was, however, denied by the patient. Patient 2 had blood everolimus levels within the therapeutic range in combination with low-dose CsA, but in spite of this a severe exacerbation of her eczema occurred.

Treatment with the macrolides sirolimus and everolimus seems to be effective in patients with psoriasis (8,9).

Non-responsiveness in our patients may be due to the fact that in contrast to AD, psoriasis is a disease characterized not only by a cutaneous influx of activated T cells, but also by hyperproliferation of keratinocytes (11,12). Therefore, the therapeutic success of everolimus in psoriasis may be explained by the presence of two therapeutic targets for everolimus (T cells and keratinocyte hyperproliferation) instead of one (T cells), as is the case in AD.

Another explanation for the non-responsiveness in our patients may be that the dosage of everolimus ($1.5 \text{ mg twice daily}$) is below the therapeutic range for AD. However, higher doses increase the incidence of serious adverse events (13).

Furthermore, blocking the synthesis of the IL-2 receptor (everolimus) may be less effective in down-regulating T-cell activation in AD than blocking IL-2 production (calcineurin inhibitors).

In spite of the encouraging results of everolimus in psoriasis, this new immunosuppressive drug does not seem to be effective in AD, either in combination with prednisone or in combination with CsA.

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