Case Report

Sirolimus and angiotensin-converting enzyme inhibitors together induce tongue oedema in renal transplant recipients

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Introduction

Sirolimus (rapamycin; SRL) is a macrocyclic lactone with a novel mechanism of immunosuppression. Via its c-7 methoxy group, SRL cross-links the immunophilin FK binding protein 12 (a peptide-prolyl isomerase that acts as a folding catalyst) to the multifunctional serine-threonine kinase, the mammalian target of rapamycin [1]. By blocking co-stimulation signals, SRL prevents the activation of the inhibitory factor, kappa kinase, necessary for the generation of the e-Rel transcription factors of the NF-κB complex, and it possibly also modulates protein kinase C activity [2]. Both the therapeutic and the toxic effects of SRL are related to the same cellular actions.

The reported pattern of the side effects of SRL in humans includes, but is not limited to, hyperlipidaemia, infections (such as Pneumocystis carinii pneumonia), headache, nausea, mild dizziness, lower limb oedema, diarrhoea, epistaxis and dose-dependent decreased platelet counts [3,4]. A single report describes an atypical oedema of the eyelid [5].

Angiotensin-converting enzyme inhibitors (ACEi) have been shown to prevent or blunt the progression of renal damage, both functional and morphological, by inducing the down-regulation of the intrarenal angiotensin II (Ang II) level through the relative inhibition of renal ACE activity [6]. The blocking of the intrarenal renin–angiotensin system (RAS), in turn, would potently contribute to the inhibition of the local formation of transforming growth factor-β 1 (TGF-β1) and the accumulation of TGF-β1-mediated extracellular matrix (ECM), both of which are related to the protective effects of ACEi on kidneys [6,7]. Ang II blockade has been recently shown to prevent the development of renal injury in animal models of chronic allograft rejection, by mechanism(s) independent of the reduction of systemic blood pressure [7,8].

These studies have demonstrated the protective effect of RAS antagonists in immunologically mediated diseases such as anti-glomerular basement membrane nephritis and chronic allograft rejection [7,8]. Furthermore, ACEi are extensively used in different clinical settings, such as hypertension, atherosclerosis and several renal diseases, in which immuno-pathogenetic mechanisms have been considered to play a crucial role.

Such observations suggested to us that the therapeutic combination of SRL and ACEi may ameliorate graft survival via a different and independent mechanism. On the other hand, the benefits of the two drugs are counterbalanced by their side effects, probably resulting from their synergic action when both drugs were administered in full doses.

We observed a particular side effect during combination therapy with SRL and ACEi in renal transplanted patients. We describe here, for the first time, the occurrence of tongue oedema in five renal transplant patients concomitantly with combined SRL and ACEi therapy.

Case

We followed 52 patients, aged between 42 and 60 years, who received a cadaveric primary renal transplant in our Outpatient Division from May 2001 to February 2002. Of these, 15 patients, older than 45 years, had received kidneys from sub-optimal donors. We define as ‘sub-optimal’ a donor who was hypertensive or older than 55 years, or both. In these patients, after induction with anti-CD25 Abs (two doses on days 0
and ACEi. Due to the persistence of the oedema, ACEi was stopped without reduction of SRL dosage. Two weeks after the discontinuation of ramipril, and without modification of SRL trough levels, the oedema resolved. Three months later (specifically, 6–8 months after transplantation), when SRL trough levels were established between 8 and 12 ng/ml, and its oral dosage between 2 and 4 mg/day, in accordance with our immunosuppressive approach for patients who had received kidneys from sub-optimal donors, ramipril at a dose of 2.5 mg/day was reintroduced in all patients. None showed side effects. At present all these patients continue their treatments with SRL and ACEi.

This particular side effect was absent in the other patients on SRL therapy and in the 37 patients on a conventional immunosuppressive protocol.

Discussion

A generalized oedematous state after renal transplantation may occur due to various factors, such as uraemic volume overload, renal function insufficient to support adequate fluid excretion, graft rejection episodes or cyclosporine toxicity. In contrast, the patients described here developed a distinct pattern of oedema limited to the tongue. However, tongue oedema may be heterogeneous. The hallmarks of a response to an allergenic xenobiotic agent are elevated eosinophilic cell counts, itching, or both. Neither of these, nor other laboratory findings were present to suggest such a response in our five patients. Various infections may be accompanied by tongue oedema, such as bacterial infiltration or viral epidemic nephropathy [9] with or without renal impairment, respectively. Rapid onset and involvement of the lips, larynx and bowel characterize the oedema of angioedema. The patients involved did not present any of these characteristics, and the time frame strictly argued against this type of disease.

The mechanism leading to the tongue oedema in our five patients is uncertain and open to speculation. Rabbit endothelial cells exposed to SRL have been shown to release increased amounts of prostacyclin, compared with those exposed to tacrolimus [10]. An excess of prostaglandins can lead to inadequate vasodilatation and thus increase fluid collection in peripheral organs; this effect may in turn be synergized by ACEi treatment which interferes with the kallikrein–kinin system [11]. Moreover, the side effect we noted occurred when full doses of SRL and ACEi were being taken; therefore, we hypothesized that the two drugs act synergistically only when full doses of both are being taken. In fact, no side effects were noted when the dose of SRL was reduced and ACEi was reintroduced at 2.5 mg/day.

Side effects of macrolide antibiotics usually appear 2–3 weeks after initiation of therapy, thus a delayed reaction to the macrocyclic compound SRL is still a possibility. Tongue oedema has not yet been reported in association with other macrocyclic compounds. This is not surprising, because the duration of therapy with macrolide antibiotics is usually shorter than with SRL. On the other hand, an adverse pharmacological reaction to enalapril has been described, with severe respiratory obstruction, secondary to lingual oedema [12]. The incidence of this condition among the population of users of this drug amounts to about 1 per thousand.

It is important to be aware of this phenomenon to avoid burdensome and costly investigations of patients showing this symptom during combination treatment with high doses of SRL and ACEi. Finally, we suggest that this symptom should not prevent...
patients from being treated with this potentially promising combination after renal transplantation.

Conflict of interest statement. None declared.

References


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