Is tacrolimus for childhood steroid-dependent nephrotic syndrome better than ciclosporin A?

Jörg Dötsch, Katalin Dittrich, Christian Plank and Wolfgang Rascher

Kinder und Jugendklinik, University of Erlangen-Nürnberg, Germany

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Immunosuppressive drugs in the treatment of severe steroid-dependent nephrotic syndrome (Figure 1)

The dosage and 3 months duration of glucocorticoid treatment in steroid-sensitive childhood idiopathic nephrotic syndrome, mainly associated with the histological picture of minimal change glomerulopathy, is based on the evidence of randomized clinical trials with clear-cut end points [1–3]. Duration of up to 7 months of the therapy may even be more effective in achieving sustained remission. A further well-designed and adequately powered randomized controlled trial is, however, required. To avoid steroid toxicity, there is convincing evidence for the use of oral cyclophosphamide in patients with frequent relapses [4]. The evidence, however, is less stable for the treatment of steroid-dependent nephrotic syndrome (SDNS), i.e. recurrence of nephrotic syndrome within 2 weeks of cessation of steroid treatment [5,6]. One of the major concerns with regard to the use of alkylating agents such as cyclophosphamide or chlorambucil in children and adolescents is gonadotoxicity [7]. Therefore, ciclosporin A (CSA) has been advocated when toxic effects of prednisone and cyclophosphamide are expected. CSA results in a remission rate of 85% in children with SDNS, bearing, however, the risk of calcineurin inhibitor-induced nephrotoxicity [8].

Thus, alternative immunosuppressive drugs such as mycophenolate mofetil [9,10], rituximab [11] and sirolimus [12] are currently under investigation. Levamisol has been found to be of benefit in SDNS and has limited toxicity [13]. Data on the use of the calcineurin inhibitor tacrolimus (TAC) are scarce.

**Is there a rationale for the use of tacrolimus in patients with SDNS?**

TAC and CSA, despite having distinct chemical structures and different cytotoxic binding proteins, have almost identical cellular effects [14]. Both lead to calcineurin inhibition in T-cells, resulting in impaired production of cytokines that are important to enable T-cell progression from the G0 to the G1 state. Therefore, at first glance, TAC does not appear to have a theoretical superiority to CSA for use in any disease, including severe SDNS. Is there still a rationale for a study examining the switch in treatment from CSA to TAC? In fact, there are some aspects in favour of performing such a study:

(i) TAC has been shown to act in a distinct, if not superior, way to CSA in children with renal transplantation [15,16].

(ii) TAC is successfully used in children with psoriasis, where CSA does not appear to be effective [17].

(iii) In adults with focal segmental glomerulosclerosis and consecutive steroid-resistant nephrotic syndrome (SRNS) remission has been induced using TAC [18].
(iv) TAC has been applied to maintain remission in eight paediatric patients with idiopathic SDNS and to induce remission in seven children with SRNS [19]. This group achieved complete remission in 81% of the patients and partial remission in 13%. However, the study is retrospective in nature, does not clearly discriminate between SDNS and SRNS and does not aim at comparing CSA and TAC.

Tacrolimus treatment after ciclosporin. A failure in children with SDNS

In this issue of the journal, Sinha and coworkers reported the switch from CSA to TAC in 10 children with severe SDNS, in whom the first drug was withdrawn for ineffectiveness or adverse effects. Nine of the patients had minimal change glomerulopathy in the initial renal biopsy, and one patient had focal segmental glomerulosclerosis. Replacing TAC for CSA did not improve:

(v) the annual relapse rate of the nephrotic syndrome (NS), and
(vi) the amount of glucocorticoids needed.

The limitation of this study is its retrospective approach and the design using TAC after CSA in a limited number of patients. Nonetheless, with respect to the data available on TAC treatment in severe childhood SDNS, the study by Sinha and coworkers is of great interest.

In our own retrospective study including five patients with severe SDNS and failure of cyclophosphamide and CSA, only one patient had a substantial improvement with TAC [20].
Adverse effects

One of the most important adverse effects of TAC is the induction of insulin-dependent diabetes mellitus (IDDM). Under immunosuppressive therapy with TAC in children after renal transplantation, the incidence of IDDM is reported to be as high as 3% [21,22]. Sinha and coworkers describe one patient who developed permanent IDDM while taking TAC. We observed IDDM in two patients with SDNS treated with TAC. Diabetes occurred when, in addition to TAC, higher prednisone doses than in post-transplant patients were used to induce remission of the nephrotic syndrome [20]. Both nephrotic patients in this study had hypoalbuminaemia. TAC binds to erythrocytes (~80%) and plasma proteins (albumin and α-1-glycoproteins) (~20%), while only the free compound (1.2%) is pharmacologically active [23,24]. In the case of hypoalbuminaemia due to the relapse of NS, there may be a reduction of the bound TAC fraction by approximately 10%, resulting in an up to 10-fold rise of the free fraction. Total blood concentrations, however, remain almost constant. It therefore seems possible that, during a relapse or sustained proteinuria, stable total TAC concentrations mask high, or even toxic, levels of the free bioactive fraction. Other adverse effects of TAC such as hypertension and nephrotoxicity appear similar to CSA.

Conclusions

There is currently no rationale for the use of TAC in place of CSA in children with SDNS and minimal change glomerulopathy, bearing in mind that all the studies performed so far are retrospective and based on a limited number of patients. In addition, the risk of drug-induced IDDM during TAC treatment of SDNS is rather discouraging.

In contrast, TAC might be more promising for the treatment of SRNS, e.g. in patients with focal segmental glomerulosclerosis [18]. Studies in this field might, therefore, be more interesting.

Conflict of interest statement. None declared.

(See related article by Sinha et al. Nephrol Dial Transplant 2006; 21:1848–1854.)

References