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ORIGINAL ARTICLE

Katalin Dittrich · Ina Knerr · Wolfgang Rascher · Jörg Dötsch

Transient insulin-dependent diabetes mellitus in children with steroid-dependent idiopathic nephrotic syndrome during tacrolimus treatment

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Abstract Despite the availability of immunosuppressive drugs such as prednisone, cyclophosphamide, cyclosporine A (CyA) and mycophenolate mofetil for the treatment of steroid-dependent idiopathic nephrotic syndrome (SDNS), medication-free remission is not achieved in a number of patients. To avoid excessive steroid toxicity, the use of tacrolimus (Tac) has been discussed. We report on five children diagnosed with SDNS on the histological basis of minimal change glomerulopathy or focal segmental glomerulosclerosis. Following the failure of other medications to achieve sustained remission, Tac was administered to these patients who varied in age from 10.5 to 13.5 years. Only one patient showed a substantial reduction in the number of relapses with the Tac treatment. Two boys, after 9 and 44 months on therapy, respectively, developed insulin-dependent diabetes mellitus (IDDM), necessitating the withdrawal of Tac and the daily use of insulin for 3 and 6 months. In both patients hyperglycemia had occurred during prednisone-based relapse therapy of SDNS. The patients had low serum protein concentrations, presumably increasing the free active Tac fraction, while trough levels of the drug remained unchanged. Both of the affected patients had additional risk factors for impaired glucose tolerance, such as morbid obesity (patient 1; BMI: 41.6 kg/m^2) and African American origin (patient 2). Our case reports demonstrate that the use of Tac in patients with SDNS may be associated with an increased risk for IDDM, especially during relapse of NS, and particularly if additional risk factors are present. Moreover, Tac does not appear to substantially increase the success of treatment.

K. Dittrich · I. Knerr · W. Rascher · J. Dötsch (✉)
Children and Adolescent Hospital,
University of Erlangen-Nürnberg,
Loschgestrasse 15,
91054 Erlangen, Germany
e-mail: Joerg.Doetsch@kinder.imed.uni-erlangen.de
Tel.: +49-9131-8533117
Fax: +49-9131-8536097

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Introduction

Tacrolimus (Tac) is a well-known pharmaceutical agent of the calcineurin inhibitor (CNI) group and commonly used following organ transplantation. It has also been shown to maintain remission in eight pediatric patients with steroid-dependent idiopathic nephrotic syndrome (SDNS) and to induce remission in seven children with steroid-resistant nephrotic syndrome (SRNS) [1] as well as to induce remission in adults with SRNS [2].

In children with SDNS, the accompanying morbidity is frequently associated with prolonged glucocorticoid therapy and cardiovascular morbidity later in life [3]. Therefore, steroid-sparing agents such as cyclophosphamide, cyclosporine A and, more recently, mycophenolate mofetil are used to reduce glucocorticoid toxicity. However, data on the use of Tac in SDNS are scarce.

The exact mechanism of Tac action on proteinuria is yet unknown. Among the side effects of Tac are those common for CNIs, such as nephrotoxicity, hypertension and hyperlipidemia. In addition, more specific adverse effects such as insulin-dependent diabetes mellitus (IDDM) have been encountered. Tac decreases the C-peptide response, and the diabetogenic effect seems to be mediated by interference with mitochondrial function of the pancreatic B-cells [4].

Tac has been reported to induce de novo IDDM in up to 8% of the adult and in 3% of the pediatric renal transplant recipients [5–7]. The manifestation of IDDM in adult patients with SRNS on Tac monotherapy has also been described [2].

Tac was used in our department for children with severe SDNS and frequent relapses under cyclosporin A (CyA) therapy. Since 1996 we have treated five patients, of whom two developed transient IDDM. Tac levels were checked once per week to once per month 12 h after last dosing with the aim of achieving Tac trough levels of 6–12 ng/ml. Blood glucose levels were determined at every outpatient visit, HbA1c was measured regularly once per 3 months.

Case reports

Case One This is a Caucasian boy in whom NS was diagnosed at the age of 2 years and who was successfully treated with standard prednisone therapy (60 mg/m^2/24 h over 6 weeks followed by 40 mg/m^2/48 h for the next 6 weeks). Frequent relapses occurred following the withdrawal of steroids.

Renal biopsy showed minimal change glomerulonephropathy (MCGN), so treatment with oral cyclophosphamide was initiated for 12 weeks (cumulative dose: 180 mg/kg). CyA therapy was initiated thereafter because of persistent steroid dependency; however, several attempts to reduce steroids failed. A second renal biopsy showed focal segmental glomerulosclerosis (FSGS) and CyA-toxicity. The patient developed signs of steroid toxicity such as severe obesity (BMI: 41.6 kg/m^2), marked bone demineralization and the absence of signs of puberty.

After a second, ineffective course of oral cyclophosphamide (cumulative dose: 100 mg/kg) and 32 relapses, treatment with Tac was started (6 mg/24 h; 0.07 mg/kg) During a period of 9 months no further relapses occurred. The 12-h trough blood levels of Tac ranged from 4.5 to 9.2 ng/ml, and the random blood glucose levels ranged from 5.7 to 11.1 mmol/l.

After 10 months of Tac therapy the patient had a relapse of NS necessitating prednisone treatment (80 mg/24 h). A few weeks later he presented with polydipsia, polyuria and a 9-kg weight loss. Blood glucose was 52.8 mmol/l, HbA1c was 13.9% (normal: 4.2–6.3%), pH 7.29, the standard base excess was −15.2 mmol/l and albumin was 28 g/dl. Ketonuria was present (Fig. 1) Antibodies against β-cells or insulin autoantibodies were not detectable. Insulin therapy was started, Tac was discontinued and a second trial of CyA was initiated. Three months later, subcutaneous insulin application could be withdrawn. The oral glucose tolerance test (OGTT) and serum insulin level were normal 22 months after the discontinuation of Tac.

Later in the course of the disease the patient was successfully treated using retuximab, as reported in an earlier publication [8].

Case Two This is an African American boy in whom NS was diagnosed at the age of 4 years and who was treated with standard prednisone regimen. After frequent relapses and ineffective treatment with oral cyclophosphamide (12 weeks; cumulative dose of 180 mg/kg), renal biopsy showed MCGN. CyA therapy was initiated and continued for 2 years.

At the age of 12 years, after 14 relapses, Tac therapy was initiated (7 mg/24 h; 0.16 mg/kg). Three relapses occurred during the 44 months on Tac therapy, all of which were treated by standard prednisone therapy. The 12-h trough blood levels of Tac ranged from 5.3 and 15.5 ng/ml.

During prednisone therapy (80 mg/24 h) for the relapses, the patient presented with hyperglycemia, polydipsia and polyuria. The BMI was 20.3 kg/m^2, blood glucose was 18 mmol/l, HbA1c was 5.5% (normal: 4.2–6.3%), serum albumin was 23 g/dl and the trough Tac level was 7.6 ng/ml (Fig. 2) Antibodies against β-cells or insulin autoantibodies were not detectable. Treatment with Tac was stopped immediately, and subcutaneous insulin therapy was carried out for 6 months. OGTT and serum insulin level were normal 8 months after the discontinuation of Tac therapy.

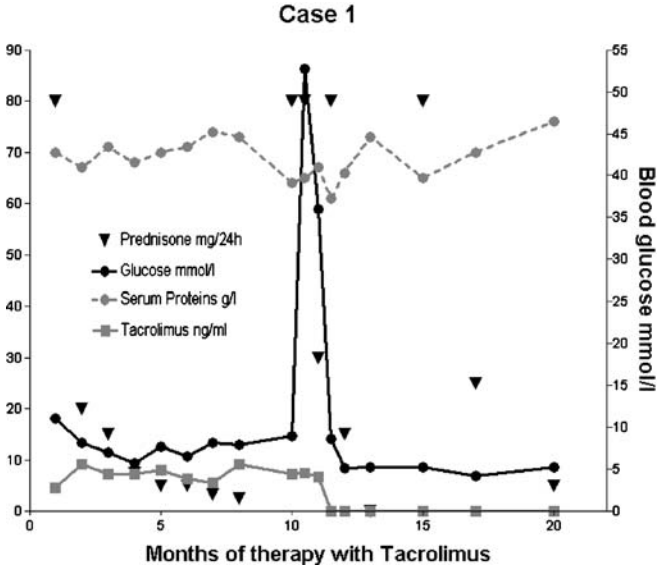

Fig. 1 Course of the therapy with Tac in case 1. A low serum protein level and a high daily dose of prednisone mark the relapse. Following the first relapse on Tac treatment, IDDM manifested with extremely high blood glucose levels and ketoacidosis. The 12-h trough Tac levels never exceeded 10 ng/ml. Insulin therapy was necessary for 3 months, and Tac was discontinued in the 11th month of treatment. The prednisone, serum protein and tacrolimus scale is given on the *left Y-axis* and the blood glucose scale is given on the *right Y-axis*

Case Three This is a Caucasian girl in whom NS was diagnosed at 19 months of age. Cyclophosphamide was administered (12 weeks; cumulative dose: 180 mg/kg) because of steroid dependency. After seven relapses, a renal biopsy showed MCGN. CyA was given for 6 years. Following 22 relapses of NS, a second renal biopsy was performed which also confirmed MCGN, and treatment with Tac (6 mg/24 h; 0.11 mg/kg) was started. Three relapses occurred during the 11 months on Tac, all of which were treated with the standard prednisone therapy. The 12-h trough blood levels of Tac ranged from 5.7 to 11.8 ng/ml; blood glucose and HbA1c levels of the obese girl (BMI: 29.7 kg/m^2) were normal. After 11 months and four relapses, Tac was withdrawn due to the failure of the patient to respond to the therapy.

Case Four This is a Caucasian girl in whom NS was diagnosed at the age of 3 years and who was subsequently treated with the standard prednisone regimen. Three relapses occurred under alternating steroid therapy. At the age of 4 years, renal biopsy showed MCGN. Cyclophosphamide (cumulative dose: 180 mg/kg) was

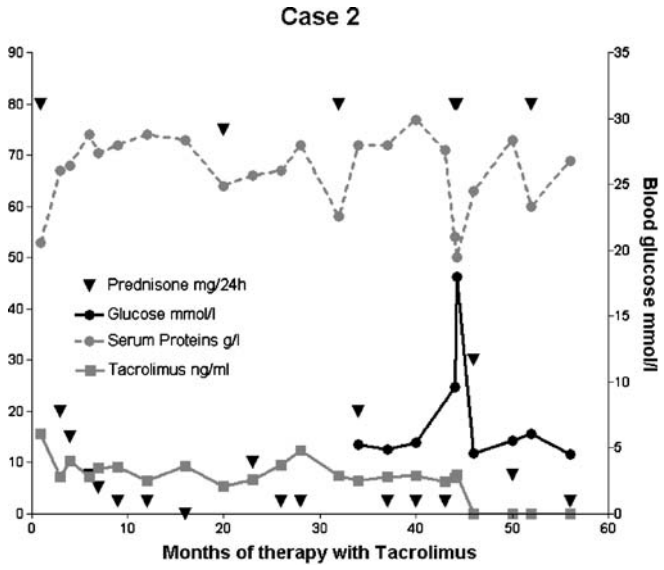

Fig. 2 Course of the therapy with Tac in case 2. Low serum protein levels and a high daily dose of prednisone mark the relapses. During the third relapse on Tac treatment, IDDM manifested with elevated blood glucose levels. The 12-h trough Tac levels were never in the toxic range. Insulin therapy was administered for 6 months, Tac was discontinued in the 44th month of treatment. The prednisone, serum protein and tacrolimus scale is given on the *left Y-axis*, and the blood glucose scale is given on the *right Y-axis*

started. A second renal biopsy revealed focal segmental sclerosis (FSGS). After the 13th relapse, a renal biopsy was once again performed (FSGS), and therapy with azathioprin (Aza) was initiated. In this phase two steroid-dependent relapses were detected, and after 3 months on Aza, CyA was added to the regimen. Aza was discontinued after 6 months, but CyA was continued for 51 months – mostly in conjunction with steroids – between the age of 9 and 13 years. In this period one to two relapses per year occurred. After the 22nd relapse, treatment with Tac at 4 mg/24 h (0.085 mg/kg) was started; this was increased up to 6 mg/24 h (0.125 mg/kg). During the 60 therapy-months on Tac four relapses occurred. The 12-h trough blood levels of Tac were between 3.5 and 14.4 ng/ml, and the blood glucose and HbA1c levels of the normal-weight girl (BMI: 19.1 kg/m^2) were always within the normal range.

Case Five This is a Caucasian boy in whom NS was diagnosed at the age of 5 years at which time a renal biopsy showed MCGN. As the patient exhibited a steroid-dependent course, CyA therapy was initiated. After 7 months and two relapses oral Cyclophosphamide therapy was given (cumulative dose: 160 mg/kg). After further relapses CyA was administered continuously between the age of 8 and 11 years. After ten relapses renal biopsy confirmed MCGN and signs of CyA toxicity. Cyclophosphamide pulse-therapy in a cumulative dose of 90 mg/kg was given, but further relapses occurred and, therefore, Tac was started at the dose of 10 mg/24 h (0.2 mg/kg). The 12-h trough blood levels of TAC ranged from 5.4 to 21.3 ng/ml, and no signs of toxicity were detected. Only one high Tac level was recorded, which resulted in a reduction of the dose to achieve trough levels between 6 and 12 ng/ml. However, two further relapses occurred, and Tac therapy was stopped after 4 months. HbA1c and blood glucose levels of this overweight boy (BMI: 24 kg/m^2) were normal on several occasions.

Discussion

TAC is not only used in transplant patients but also in patients with NS [1, 2]. It acts as a calcineurin inhibitor in affecting IL-2 gene activation. Since T-cells are attributed to have an important role in the pathogenesis of NS, the inhibition of T-cell function by attenuating IL-2 production can result in clinical improvement.

We report here our observations on five children with SDNS for whom, despite therapy with cyclophosphamide and CyA, it was necessary to use Tac. At the time of treatment, mycophenolate mofetil had not yet been proposed for the treatment of SDNS. Two of the five patients developed de novo IDDM requiring insulin therapy for more than 30 days. In addition to the high number of severe side effects, only one of the five patients had a substantial improvement – i.e. a substantial reduction in the number of relapses.

The incidence rate of IDDM in pediatric patients who have undergone renal transplantation and are under immunosuppressive therapy has been reported to be as high as 3% [6, 7]. Impaired glucose tolerance following transplantation can be due to either a reversible, dose-dependent toxic effect of Tac on the pancreatic β-cells [4], without morphological changes of the pancreas [9], or co-medications leading to the requirement of exogenous insulin.

We observed IDDM in two patients with SDNS treated with Tac following relapse necessitating the use of higher prednisone doses than those normally administered to post-transplant patients. In addition, both nephrotic patients had hypoproteinemia/hypoalbunimemia. It is known that Tac binds to erythrocytes and plasma proteins (albumin and alpha-1-glycoproteins) at an efficiency of up to 98.8%, while only the free compound (1.2%) is pharmacologically active [10, 11]. Since up to 80% of Tac binds to erythrocytes and approximately 20% binds to proteins such as albumin and alpha-1 glycoprotein [10, 11], in the case of hypoalbuminemia resulting from the relapse of NS, there may be a reduction in the bound Tac fraction by approximately 10% along with an up to tenfold rise in the level of the free fraction. Total blood concentrations, however, remain almost constant. It therefore seems possible that during a relapse stable Tac concentrations mask high, or even toxic levels of the free bioactive fraction due to a reduced concentration of plasma protein.

Other risk factors for the manifestation of DM following kidney transplantation include race (relative risk of African Americans vs. Caucasian Americans: 1.68), obesity (relative risk of BMI >30 vs. <30 kg/m^2: 1.73) and gender (relative risk of males vs. females: 1.12) in adult and

pediatric patients [6, 12]. In our cohort, both patients with IDDM were male: patient 1 had severe obesity and patient 2 is from African American origin.

In conclusion, the purpose of this report is to stress the significance and risk factors of therapy-induced IDDM during Tac treatment of SDNS. In addition, we have found that the effect of Tac is not substantially superior to that of cyclosporin A.

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