No Significant Influence of Reduced Initial Tacrolimus Dose on Risk of Underdosing and Early Graft Function in Older and Overweight Kidney Transplant Recipients

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ABSTRACT

Background. Nowadays, a reduced initial daily dose of tacrolimus (Tac) (0.1–0.15 mg/kg) is recommended for the majority of kidney transplant recipients (KTRs). The aim of the study was to analyze the safety of such a regimen, including the risk of first inadequately low Tac blood level, acute rejection (AR) occurrence, or early graft dysfunction.

Methods. In 2011, we introduced a modified (0.1–0.15 mg/kg/d) initial Tac dosing regimen in older (>55 years) and/or overweight KTRs. To assure the safety of this protocol, we monitored the risk of inadequately low blood Tac level (<6 ng/mL) and incidence of AR or delayed graft function (DGF). The historical cohort with the higher Tac dosing regimen (0.2 mg/kg/d, n = 208) served as a control group.

Results. The mean Tac daily dose in 78 KTRs (group with reduced dosing) was 0.133 (95% confidence interval [CI], 0.130–0.136) mg/kg and was significantly lower than the standard, previously prescribed dose of 0.195 (95% CI, 0.194–0.197) mg/kg. Of note, induction therapy was employed twice more often in the reduced Tac dosing group. The dose reduction resulted in a slight, nonsignificant decrease in first Tac trough level. The percentages of patients with first Tac troughs <6 ng/mL (5.1% vs 4.8%), AR (6.4% vs 5.8%), and DGF (25.6% vs 31.2%) were similar in the reduced and standard dosing groups.

Conclusion. The currently recommended reduction in Tac initial dosing does not increase the risk of inadequate immunosuppression and does not affect the early graft function. Regardless of Tac dose reduction, there is still a substantial risk of Tac overdosing in older or overweight KTRs.

NOWADAYS, tacrolimus (Tac), a calcineurin inhibitor, is the most commonly used immunosuppressive drug in kidney transplantation. The substantial inter- and intrapatient variability of dose requirement to achieve accurate Tac target blood concentrations and its narrow therapeutic index result in the need for careful blood Tac concentration monitoring, and subsequent dose adjustment [1–3]. The wide spectrum of Tac's adverse effects includes delayed graft function (DGF), thrombotic microangiopathy, diabetes, increased burden of infections, neurologic toxicity, and direct injury to graft vasculature [4–9]. On the other hand, inappropriately low Tac levels may lead to increased incidence of early acute rejection episodes and DGF [10,11].

From the beginning of its clinical use in the kidney transplantation setting, the recommended initial Tac dose was fixed at 0.2 mg/kg/d (as given in Summary of Product Characteristics). In the United States, this starting dose was

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later reduced to 0.1–0.15 mg/kg/d in patients receiving basiliximab induction or treated with mycophenolate mofetil. At our center, based on previous clinical observations, since 2011 we have utilized a modified (reduced from 0.2 to 0.1–0.15 mg/kg/d) initial Tac dosing regimen in older (>55 years) and/or overweight kidney transplant recipients (KTRs), as these patients were found to have an increased risk of Tac overdosing and toxicity.

The aim of this study was to assess the safety of the aforementioned protocol based on the risk of inadequately low first blood Tac level (<6 ng/mL) and an incidence of DGF or early posttransplant acute rejection. The historical cohort of corresponding—that is, older or overweight kidney graft recipients—treated with the higher dose regimen of Tac (0.2 mg/kg/d) served as a control group.

MATERIALS AND METHODS

Study Group

Eight hundred eighty-seven consecutive adult KTRs operated at our center between 2000 and 2017, who were initially treated with an immunosuppressive regimen containing twice-daily Tac, were identified in the center transplant database. Among the cohort, 286 overweight/obese and/or >55-year-old patients were included in this analysis. The bioethics committee of the Medical University of Silesia granted permission to keep the register and also to perform this analysis based on anonymously analyzed data. Informed consent was not necessary, as the data analysis does not meet the criteria of a medical experiment.

Immunosuppression

After transplantation, most of the patients received triple immunosuppression therapy, which consisted of Tac, mycophenolate mofetil or azathioprine or sirolimus, and steroids. The initial Tac dose (in general, 0.2 mg/kg/d) was already given orally before the transplantation procedure, and then twice daily. In 2011, we introduced a modified (reduced from 0.2 to 0.1–0.15 mg/kg/d) initial Tac dosing regimen in older (>55 years) and/or overweight KTRs. Steroids were used in all patients, starting with 500 mg methylprednisolone (intravenously) during the operating procedure, 125 mg on the first posttransplant day, and then 20 mg prednisone orally every morning. A total of 94 patients received basiliximab (Simulect; Novartis, Basel, Switzerland) as induction therapy.

In all analyzed patients, the first Tac blood level determination was performed in the morning, at least 24 hours after the transplantation procedure. Blood samples for Tac trough level assessments were withdrawn 12 hours after the evening dose. Tac concentrations were assessed using the microparticle enzyme immunoassay (MEIA; Abbott Laboratories, Abbott Park, IL). The upper limit was set at 30 ng/mL, and all values exceeding this result were encoded in the database as 30 ng/mL.

Data Analysis

Nutritional status was scored according to World Health Organization criteria, based on anthropometric measurements performed immediately before the transplantation procedure (overweight: body mass index [BMI] 25–29.9 kg/m^2; obese: BMI ≥30 kg/m^2).

Initial graft function was defined as immediate (IGF), slow (SGF), or delayed (DGF). IGF was defined as serum creatinine concentration (sCr) on the third posttransplant day of ≤264 μmol/L (3 mg/dL), SGF was defined as sCr >264 μmol/L on the third posttransplant day, and DGF was defined as the need for dialysis therapy during the first week after transplantation.

In this analysis, we included all early acute rejection episodes diagnosed during the first posttransplant hospitalization, which ranged from 8 to 69 days (mean, 21 days).

Statistical Analysis

The size of the study group (reduced Tac dosing) was not established based on the power analysis. Statistical analyses were performed using STATISTICA version 10.0 PL for Windows (StatSoft Polska, Kraków, Poland) and MedCalc version 12.3.0.0 (MedCalc, Mariakerke, Belgium). Values are presented as mean and 95% confidence interval (CI) or as frequency. The initial comparison was performed for subgroups defined by reduced or standard initial Tac dosing. The subgroups were compared using the chi-square test (qualitative variables) and analysis of variance (ANOVA; quantitative variables). For all statistical tests, $P < .05$ was considered statistically significant; however, for multivariate analyses, a P value between 0.05 and 0.1 was interpreted as borderline significant.

RESULTS

The study group with reduced initial Tac dosing consisted of 78 KTRs, who had received a mean dose of 0.133 (95% CI, 0.130–0.136) mg/kg. That was lower, by 32%, in relation to the standard, previously prescribed dose of 0.195 (95% CI, 0.194–0.197) mg/kg. The group with reduced dosing was characterized by significantly higher BMI and different gender distribution—with a greater prevalence of men (Table 1). There was also significantly fewer mismatches for human leukocyte antigen (HLA) class II, and a 2-fold higher percentage of patients treated with induction therapy.

The initial dose reduction resulted in slight (6.0%) and nonsignificant decreases in first blood Tac trough level (15.6 [13.9–17.3] vs 16.6 [15.6–17.6] ng/mL). There was also no significant difference in prevalence of potentially subtherapeutic (<6 ng/mL) first Tac level (5.1% vs 4.8% in the standard dosing group). The incidence of early acute rejection (6.4% vs 5.8%) was similar in the 2 groups (Fig 1). Despite Tac dose reduction, the incidence of DGF did not improve significantly (25.6% vs 31.2%), and the percentage of patients with immediate graft function was similar (20.5% vs 21.1%) (Fig 1). Of note, none of the primary nonfunctioning kidney grafts in the 2 groups were lost due to thrombotic microangiopathy or biopsy-proven acute Tac toxicity.

Moreover, we did not observe a marked reduction in the potentially supratherapeutic (>15 ng/mL) Tac levels (44.9% vs 51.4% in the reduced and standard dosing groups, respectively).

DISCUSSION

In this study we have shown that our strategy of reduced initial Tac dosing in a subgroup of recipients >55 years of age or overweight/obese subjects to 0.1–0.15 mg/kg/d did not increase the risk of inadequate immunosuppression in