Differences in the Incidence and Clinical Evolution of Early Neurotoxicity After Liver Transplantation Based on Tacrolimus Formulation Used in the Immunosuppressive Induction Protocol

R. Souto-Rodríguez, E. Molina-Pérez*, J.F. Castroagudín, A. Fernández Pérez, E. Otero-Antón, S. Tomé Martínez de Rituerto, J. Martínez-Castro, and E. Varo-Pérez

Abdominal Trasplant Unit, Universitary Clinical Hospital, Santiago de Compostela, Spain

ABSTRACT

Introduction. Posttransplant early calcineurin inhibitor (CNI)-induced neurotoxicity (ECIIN) was related to high CNI levels, among other factors. Minimizing exposure could modify its incidence or clinical evolution.

Objective. To compare the incidence, predisposing factors, and clinical evolution of ECIIN after immunosuppressive induction with low-dose tacrolimus-MR (Advagraf) or conventional dose tacrolimus (Prograf).

Patients and Methods. We matched 71 patients treated with an immunosuppression induction schedule with basiliximab and low doses of Advagraf (cases group) 1:1 by recipient age and indication for liver transplantation (OLT) with patients treated with a conventional tacrolimus regimen (control group). Baseline characteristics, liver and kidney function, operative technical characteristics, kidney function, and C_0 tacrolimus levels at several time points after liver OLT were analyzed.

Results. There were 31 cases of ECIIN (21%), 14 in the cases group (20%) and 17 in the control group (24%; $P < .001$). The incidence of ECIIN was higher in alcoholic liver disease (odds ratio [OR], 8.2; 95% CI, 2.3–28.6; $P < .001$) and past history of encephalopathy (OR, 2.6; 95% CI, 1.16–5.9; $P < .02$). Among cases, the incidence of ECIIN was higher when encephalopathy signs were present at time of transplantation (36% vs 12%; $P < .001$). Control of ECIIN required a switch to cyclosporine therapy in all those in the cases group, whereas this was only needed for 9 cases in the control group (47%; $P < .001$).

Conclusion. In this study, although the incidence rate of neurotoxicity induced by Advagraf was lower than the induced by Prograf, it did not respond to routine treatment and required a significantly higher rate of switch to cyclosporine for its control.

CALCINEURIN INHIBITORS (CNI) are the cornerstone immunosuppressive agents after orthotropic liver transplantation (OLT). Tacrolimus in the twice-daily formulation (Prograf Astellas Pharma Europe Ltd, Staines, UK) is usually the basis of the induction regimen. A new formulation has enabled once daily dosing (Advagraf Astellas Pharma Europe Ltd, Staines, UK), and has been licensed for use [1]. In addition to better adherence to immunosuppression therapy [2], the achievement of similar area under the concentration–time curve from 0 to 24 hours post dose (AUC_{24}) with a lower C_{max} could be a protective strategy against CNI-induced nephrotoxicity [3]. To minimize the exposure to CNI, the immunosuppressive induction schedule was modified in our center, using basiliximab, tapering corticosteroids regimen, and low doses of Advagraf as CNI formulation.

Early CNI-induced neurotoxicity (ECIIN) is among the adverse events with a greater impact after OLT, worsening

*Address correspondence to Ester Molina-Pérez, Complejo Hospitalario Universitario de Santiago de Compostela. Unidad de trasplante abdominal. Choupana sn. 15896 Santiago de Compostela, Spain. E-mail: esther.molina.perez@sergas.es

360 Park Avenue South, New York, NY 10010-1710

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quality of life and lengthening hospital stay [4]. Furthermore, dose modification or switch of immunosuppressive therapy necessary for control of neurologic symptoms may cause an increased incidence of acute rejection, grafts dysfunction and infections [5]. Vasogenic edema is among the proposed mechanisms involved in the pathogenesis of CNI-induced neurotoxicity [6], so that a minor change in C_{max} could modify its incidence or progression.

The objective of this study was compare the incidence rate, predisposing factors, and clinical evolution of ECIIN after immunosuppression induction with low doses of tacrolimus-MR (Advagraf) or conventional doses of tacrolimus (Prograf).

PATIENTS AND METHODS

We designed a matched, case-control study recording baseline characteristics, pretransplant liver and kidney function parameters, operative technical characteristics, kidney function after OLT, and tacrolimus levels during the first month after OLT. Seventy-one consecutive liver patients recipients (cases group) treated from February 2011 to December 2012 with an immunosuppressive induction regimen using basiliximab (20 mg in days 1 and 4 posttransplantation), a standard tapering steroids schedule and low doses of Advagraf (0.1 mg/kg per day in a dose) were included. Each case was matched 1:1 with an historic consecutive control according receptor age and indication (control group), induced with Prograf (0.1 mg/kg per day in 2 divided doses) plus steroids in similar schedule. The parameters analyzed in both groups are shown in Table 1.

Diagnosis of ECIIN was made, according to definition, when a patient developed confusion, agitation, altered level of consciousness, seizure, psychosis, focal symptoms, coma, or leukoencephalopathy, in the absence of a neurologic lesion in the first month after OLT and, usually, improving with modification dose of CNI [7]. We also recorded switch of CNI rate, time to conversion, acute rejection graft rate within 3 months after conversion, infection rate, and neurologic sequelae.

Data were analyzed by habitual statistical tests, using the McNemar test for matched samples to compare ECIIN, acute rejection, and infection rate after OLT. The results are shown as percentages, odds ratio, and 95% CIs. The level of significance was 5% (2-sided test).

RESULTS

We analyzed 142 patients (120 men and 22 women) who underwent liver transplantation at a mean age of 56.2 ± 8.3 years, with a Model for End-stage Liver Disease score of 13.1 ± 5.4. Alcoholic cirrhosis was present in 86 cases (61%) and viral cirrhosis in 30 (21%). Fifty-six patients (38%) had a past history of encephalopathy, with 34 presenting (23%) with clinical signs at transplantation. There were no differences in the baseline, technical characteristics, or donor age between cases and controls, except for pretransplantation sodium levels ($P < .01$). Posttransplantation, lower sodium level at day 7 (136 ± 6 vs 140 ± 4; $P < .01$) and higher creatinine level at day 30 after OLT (1.3 ± 0.5 vs 1.1 ± 0.4 mg/dL; $P < .01$) were observed in the control group (Table 1).

Thirty-one cases of ECIIN (20.9%) occurred, 14 (19.7%) among cases and 17 (23.9%) among group. On univariate analysis, ECIIN was significantly associated with alcoholic liver disease, past history of encephalopathy, and pretransplant level of sodium ($P > .01$). On multivariate analysis, only alcoholic liver disease was significantly associated with ECIIN (OR, 15.4; 95% CI, 1.6–147.5; $P = .02$). Patients with signs of encephalopathy at the time of transplantation time were at greater risk for developing ECIIN when Advagraf was used in the induction schedule (35.7% vs 11.8%; OR, 0.3; 95% CI, 0.01–0.8; $P < .001$). We did not observe other predisposing factors to ECIIN among cases versus controls, including tacrolimus levels. To control ECIIN clinically, all patients who underwent induction with Advagraf needed switch to cyclosporine; however, this switch was necessary in only 9 of those who underwent induction with Prograf (52.9%). Furthermore, time to conversion when ECIIN has developed was significantly lower in the cases group (12.6 ± 4.0 vs 18.9 ± 5.6; $P < .01$). Neurologic sequelae occurred only in 2 patients in the cases group versus none in the control group.

Although the overall acute rejection rate was not different between patients with or without ECIIN (9 vs 21%), among those who developed ECIIN, it was higher in patients induced with Advagraf versus those induced with Prograf (42.9% vs 17.6%), although without significant difference. Infection rate were similar in both groups.

DISCUSSION

CNI-induced neurotoxicity is among the more debilitating adverse events after OLT, with a prevalence rate of 6% to 47% of recipients treated with CNI-based immunosuppression [7]. Clinical manifestation range from mild tremor to an early, severe syndrome defined by confusion, agitation, altered level of consciousness, seizure, psychosis, focal symptoms, coma, or leukoencephalopathy, and in absence of other neurologic lesion (ie, ECIIN) [8]. ECIIN is considered as the most frequent adverse event leading to dose modification and switching the immunosuppressive regimen [9]. One factor involved in the pathogenesis of CNI-induced neurotoxicity is vasogenic edema caused by constriction of brain capillaries, which may be related to the C_{max} of CNI [6].

A new formulation of tacrolimus, enable once daily dosing, is available now. This formulation is bioequivalent to standard tacrolimus, twice daily dosing, with a lower C_{max} and relative lower values of AUC_{24} [10]. This reduction in AUC_{24} seem be increased in induction schedule, requiring higher doses of Advagraf to a maintain similar C_{min} as with Prograf [11]. This reduction, in addition to a lesser C_{max}, could have a protective effect in adverse events related to the exposure to and peak levels of CNI, like nephrotoxicity or neurotoxicity.

We have compared in a matched case-control study the incidence rate, predisposing factors, and clinical evolution of ECIIN after immunosuppression induction with low-dose Advagraf (cases) or a conventional dose of Prograf (controls). ECIIN was diagnosed in 31 patients (20.9%). This rate could be explained by the high number of patients with a past history of alcoholic cirrhosis (60%) and encephalopathy