International Immunopharmacology 39 (2016) 192–198

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

5-year follow-up of a randomized clinical study comparing everolimus plus reduced-dose cyclosporine with mycophenolate mofetil plus standard-dose cyclosporine in de novo kidney transplantation: Retrospective single center assessment

Takahisa Hiramitsu [a,*], Manabu Okada [a], Kenta Futamura [a], Takayuki Yamamoto [a], Makoto Tsujita [a], Norihiko Goto [a], Shunji Narumi [a], Yoshihiko Watarai [a], Asami Takeda [b], Kenta Iwasaki [c], Kazuharu Uchida [d], Takaaki Kobayashi [d,*]

[a] Nagoya Daini Red Cross Hospital, Department of Transplant and Endocrine Surgery, 2-9 Myoken-cho, Showa-ku, Nagoya 466-8650, Japan
[b] Nagoya Daini Red Cross Hospital, Department of Nephrology, 2-9 Myoken-cho, Showa-ku, Nagoya 466-8650, Japan
[c] Aichi Medical University School of Medicine, Department of Kidney Disease and Transplant Immunology, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan
[d] Aichi Medical University School of Medicine, Department of Renal Transplant Surgery, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan

ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 26 June 2016
Accepted 18 July 2016
Available online 2 August 2016

Keywords:
Reduced-dose cyclosporine
Everolimus
Renal transplantation

ABSTRACT

The aim of this study is to evaluate the efficacy and safety of everolimus plus reduced-dose cyclosporine compared with mycophenolate mofetil plus standard-dose cyclosporine 5 years after living donor kidney transplantation.

Between March 2008 and August 2009, 24 living donor kidney transplantations were enrolled in a 2-year, multicenter, randomized phase 3 study (RAD001A1202 study). 24 recipients were randomly classified into two groups and closely observed for 5 years. 13 recipients were administered steroid, reduced-dose cyclosporine, everolimus and basiliximab (EVR group). 11 recipients were administered steroid, standard-dose cyclosporine, mycophenolate mofetil and basiliximab (STD group). Two groups were compared not only in graft function including estimated glomerular filtration rate (eGFR), and proteinuria, but also in adverse events such as de novo donor-specific antibody (DSA) production, rejection, new-onset diabetes, hyperlipidemia, and cytomegalovirus (CMV) infection.

No graft loss was identified in 5 years. The incidences of acute T cell rejection, de novo DSA production, hyperlipidemia, and new-onset diabetes were similar. eGFR levels throughout the observation periods were similar. Three cases of proteinuria were identified in STD group. One case of proteinuria observed in EVR group was well controlled with angiotensin receptor blocker. Incidence of CMV infection in CMV antibody-positive recipients was significantly lower in EVR group.

The safety and efficacy of reduced-dose cyclosporine and everolimus protocol were similar to those of standard-dose cyclosporine and mycophenolate mofetil other than for superior prevention of CMV infection.

1. Introduction

For the optimal long-term transplanted kidney function, non-nephrotoxic immunosuppressive protocol is preferable [1,2]. Conversion of calcineurin inhibitor to everolimus was considered to be one of the best options. ZEUS study reported that cyclosporine conversion to everolimus 4.5 months after transplantation increased the incidence of biopsy-proven acute rejection at 12 months [3]. On the other hand, graft function was significantly superior after cyclosporine conversion to everolimus at 12 months. The incidences of herpes virus infection, thrombocytopenia, aphthous stomatitis were more frequent after cyclosporine conversion to everolimus, whereas cytomegalovirus (CMV) infection did not increase. The use of lipid-modifying drugs due to hyperlipidemia was more frequent in patients with cyclosporine conversion to everolimus. Urinary protein excretion increased significantly after cyclosporine conversion to everolimus [3]. In 5-year follow-up of ZEUS study, the graft function was significantly superior in patients with cyclosporine conversion to everolimus. Incidence of de novo donor-specific antibody (DSA) production was also reported to be similar [4].

Abbreviations: DSA, de novo donor-specific antibody; eGFR, estimated glomerular filtration rate; CMV, cytomegalovirus; STD, standard-dose cyclosporine with mycophenolate mofetil; EVR, reduced-dose cyclosporine with everolimus.

* Corresponding authors.
E-mail addresses: thira@nagoya2.jrc.or.jp (T. Hiramitsu), takaaki.kobayashi@aichi-med-u.ac.jp (T. Kobayashi).

http://dx.doi.org/10.1016/j.intimp.2016.07.019
1567-5769/

On the other hand, increased incidence of de novo DSA production in the calcineurin inhibitor conversion to everolimus was reported, although the mean observation periods and the median time between kidney transplantation and conversion to everolimus were different from those of ZEUS study [5]. To reduce the biopsy-proven acute rejection within the first year and to gain better outcome, protocol of reduced calcineurin inhibitor with everolimus was investigated. The efficacy of reduced-dose cyclosporine with everolimus on the de novo kidney transplantation was compared to that of standard cyclosporine with mycophenolate mofetil within 3-year follow-up [6–10]. Although reduced-dose cyclosporine with everolimus did not increase the rejection rate, reduced-dose cyclosporine with everolimus demonstrated a high risk of hyperlipidemia, proteinuria, and new on-set diabetes [6–10]. The incidence of CMV infection was significantly lower in reduced-dose cyclosporine with everolimus [6–12]. However, the estimated glomerular filtration rate (eGFR) made no significant difference between two protocols [8–10]. There are a few reports on long-term effects of reduced dose cyclosporine in combination with everolimus. Detailed assessment of medium-term (5-year) effects of everolimus-based regimen on renal function and adverse effects including eGFR, de novo DSA production, rejection, diabetes, and hyperlipidemia remain to be investigated. Here, we report 5-year follow-up of randomized clinical study (A1202 study) on everolimus-based regimen in a single center.

2. Methods

2.1. Ethical review

Written informed consent was obtained from all study patients. This study was approved by the Institutional Review Board of Nagoya Daini Red Cross Hospital and by the Institutional Ethics Committee of Aichi Medical University School of Medicine in accordance with the current standard for human research (the Declaration of Helsinki).

2.2. Study design

To investigate the medium-term effect of reduced-dose cyclosporine with everolimus (EVR group) compared to standard cyclosporine with mycophenolate mofetil (STD group), estimated glomerular filtration rate (eGFR) and adverse events including de novo donor-specific antibody (DSA) production, rejection, new-onset diabetes, hyperlipidemia, and CMV infection were investigated. This is a retrospective cohort study in accordance with STROBE guidelines.

2.3. Participants

Between March 2008 and August 2009, 24 living donor adult kidney transplantations performed at our hospital were enrolled in a 2-year, multicenter, randomized phase 3 study (RAD001A1202 study). 13 recipients were assigned to EVR group and 11 recipients were assigned to STD group (Fig. 1). They were observed every month between March 2008 and October 2015 (mean observation period: 73.3 ± 15.5 months). All patients' data were retrospectively collected from their medical records without missing data.

2.4. Statistical analysis

Statistical analyses were performed using the independent samples *t*-test or Mann-Whitney *U* test for continuous data and χ^2 or Fisher's exact test for the categorical variables. *p*-Values < 0.05 were considered statistically significant. Analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL, USA) statistical software.

2.5. Induction protocol for EVR and STD groups

All recipients were additionally treated with steroids and basiliximab. 13 recipients assigned to EVR group were administered cyclosporine 3 mg/kg b.i.d. and everolimus 0.75 mg b.i.d. The target range of everolimus was 3–8 ng/ml in trough level. Trough levels of cyclosporine were targeted to 100–200 ng/ml within 2 months, 75–150 ng/ml between 2 and 4 months, 50–100 ng/ml between 4 and 6 months, and 25–50 ng/ml after 6 months. 11 recipients assigned to STD group were administered cyclosporine 4 mg/kg b.i.d. and mycophenolate mofetil 1000 mg b.i.d. The target ranges of cyclosporine in trough were 200–300 ng/ml within 2 months, and 100–250 ng/ml after 2 months. Mycophenolate mofetil was maintained throughout the observation period, if adverse effects were not identified due to the over immunosuppression.

2.6. Follow-up

During the observation period, routine kidney graft biopsy was conducted at 6 months and 1 year after transplantation. Occasional kidney graft biopsy was performed when the creatinine level increased and proteinuria was identified. Prophylaxic valganciclovir was not administered, whereas CMV antigen (pp65: antigenemia method) was examined in every check-up within one year. CMV infection manifesting CMV viremia and disease with attributed symptoms was treated with

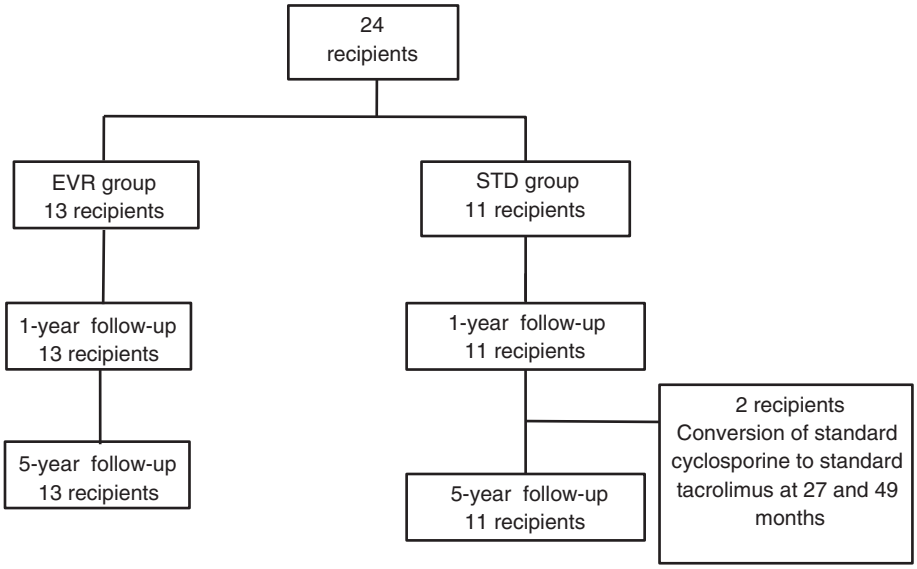

Fig. 1. Patients' flow chart.