

Similar Efficacy and Safety of Enteric-coated Mycophenolate Sodium (EC-MPS, Myfortic) Compared With Mycophenolate Mofetil (MMF) in De Novo Heart Transplant Recipients: Results of a 12-Month, Single-blind, Randomized, Parallel-group, Multicenter Study

Jon A. Kobashigawa, MD,^a Dale G. Renlund, MD,^b Gino Gerosa, MD,^c Luis Almenar, MD,^d Howard J. Eisen, MD,^e Anne M. Keogh, MD,^f Hans B. Lehmkuhl, MD,^g Ugo Livi, MD,^h Heather Ross, MD,ⁱ Javier Segovia, MD,^j and Nizar Yonan, MD^k on behalf of the ERL2401 Heart Study Investigators

Background: Enteric-coated mycophenolate sodium (EC-MPS, myfortic) is an advanced formulation that delays the release of mycophenolic acid (MPA). Its efficacy and safety has been proven in several clinical trials in renal transplantation.

Methods: In a single-blind, multicenter trial, a total of 154 de novo heart transplant patients were randomized to either EC-MPS 1,080 mg twice daily or mycophenolate mofetil (MMF) 1,500 mg twice daily. Eligible patients included men or women aged 18 to 65 years, undergoing primary heart transplantation, who were treated with cyclosporine microemulsion and corticosteroids as basic immunosuppression. The primary study objective was to investigate the incidence of biopsy-proven and treated acute rejection, graft loss or death (defined as treatment failure) for EC-MPS vs MMF during the first 6 months of treatment in de novo heart transplant recipients. Secondary objectives included assessment of the overall safety and tolerability of EC-MPS vs MMF in the study population.

Results: The primary efficacy variable, treatment failure at 6 months, was similar for both treatments: 52.6% for EC-MPS and 57.9% for MMF (2-sided 95% confidence interval [CI]: -21.0% to 10.4%). At 12 months, treatment failure was 57.7% for EC-MPS and 60.5% for MMF (2-sided 95% CI: -18.4 to 12.7), and death and graft loss rate was 5.1% vs 9.2% for EC-MPS and MMF at 12 months, respectively (2-sided 95% CI: -12.2 to 4.1). The overall safety profile was similar for both groups. Significantly more patients on MMF had two or more study medication dose reductions during the treatment period.

Conclusions: These 6- and 12-month results show that EC-MPS is therapeutically similar to MMF in de novo heart transplant recipients and has a comparable safety profile. *J Heart Lung Transplant* 2006;25:935-41. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

In heart transplantation, a multi-tiered approach to immunosuppression decreases the vigor of the alloimmune response. Different molecular aspects of the rejection cascade are targeted and lower doses of more than one drug are employed to reduce specific toxicities and to optimize synergistic immunosuppression.

The three major classes of drugs used are corticosteroids, calcineurin inhibitors (CNIs) and anti-proliferative or anti-metabolic agents.

Although numerous anti-proliferative and anti-metabolic drugs have been used in heart transplantation over the years, the commonly employed ones are

From the ^aDepartment of Cardiology, University of California at Los Angeles, Los Angeles, California; ^bLDS Hospital, Heart Failure Treatment and Prevention, University of Utah, Salt Lake City, Utah; ^cPoliclinico, Università degli Studi, Istituto di Chirurgia Cardiovascolare, University of Padova, Padova, Italy; ^dHospital La Fe, Valencia, Spain; ^eDivision of Cardiology, Drexel University College of Medicine, Philadelphia, Pennsylvania; ^fCT Transplant Unit, St. Vincent's Hospital, Sydney, Australia; ^gDeutsches Herzzentrum Berlin, Berlin, Germany; ^hDepartment of Cardiovascular Sciences, Azienda Ospedale, Udine, Italy; ⁱToronto General Hospital, Toronto, Ontario, Canada; ^jUnidad de Trasplante Cardíaco, Hospital Universitario Puerta de Hierro, Madrid, Spain; and ^kCardiothoracic Transplant Centre, Wythenshawe Hospital, Manchester, UK.

Submitted December 15, 2005; revised April 13, 2006; accepted April 17, 2006.

Supported by Novartis AG.

Reprint requests: Jon A. Kobashigawa, MD, Division of Cardiology, David Geffen School of Medicine, University of California at Los Angeles, 100 UCLA Medical Plaza, #630, Los Angeles, CA 90095. Telephone: 310-794-1200. Fax: 310-794-1211. E-mail: jonk@mednet.ucla.edu

Copyright © 2006 by the International Society for Heart and Lung Transplantation. 1053-2498/06/\$-see front matter. doi:10.1016/j.healun.2006.04.005

inhibitors of purine biosynthesis and of the mammalian kinase, target of rapamycin, a key enzyme in cell-cycle progression.¹ Inhibitors of purine biosynthesis include the anti-metabolite, azathioprine (AZA), and inhibitors of inosine monophosphate dehydrogenase. B and T lymphocytes are highly dependent on the *de novo* pathway for purine biosynthesis for cell proliferation, whereas other cell types can use salvage pathways.

Inhibitors of inosine monophosphate dehydrogenase, which selectively inhibits lymphocyte proliferation and functions (including antibody formation, cellular adhesion and migration),² depend on the action of mycophenolic acid (MPA). Mycophenolate mofetil (MMF), which is metabolized in the body to MPA, is used in the majority of heart transplant recipients to prevent cardiac allograft rejection, typically in combination with corticosteroids and a CNI.³ In cardiac transplantation, MMF has been widely accepted because of its excellent efficacy and acceptable safety profile. The principal toxicities are gastrointestinal and hematologic. The gastrointestinal toxicity includes diarrhea, nausea, vomiting, gastritis and anorexia.⁴ Unfortunately, the dose reductions or interruptions necessary to decrease these side effects may lead to sub-therapeutic exposure to MPA.⁵

In an attempt to avoid gastrointestinal toxicity-related dose reductions or interruptions, an advanced formulation of mycophenolate sodium has been developed that reliably delivers MPA, the active moiety. This new formulation, enteric-coated mycophenolate sodium (EC-MPS), has the potential to improve the therapeutic window of MPA and thus enabling a more steady mycophenolate exposure with the possibility to avoid or reduce the number of dose reductions. Clinical trials in renal transplantation have demonstrated efficacy and safety of EC-MPS and suggest that it may be better tolerated than MMF.^{6,7}

The purpose of the present study was to compare the efficacy and the safety of EC-MPS and MMF in *de novo* heart transplant recipients. In addition, the study sought to determine whether the gastrointestinal side effects that occasionally limit the ability to achieve optimal dosing with MMF could be mitigated by use of EC-MPS.

METHODS

One hundred fifty-four primary heart transplant patients, aged 18 to 65 years, were enrolled over 16 months in this 12-month, single-blind, randomized, multicenter, parallel-group study of the efficacy, safety and tolerability of EC-MPS (78 patients) vs MMF (76 patients). Patients from 26 centers were randomized at a 1:1 ratio within 72 hours after transplantation to either 2,160 mg/day EC-MPS (1,080 mg twice a day) or 3,000 mg/day MMF (1,500 mg twice a day)—that is, equimolar MPA doses—as part of a triple immunosup-

pressive therapy utilizing cyclosporine microemulsion (CsA; recommended starting dose 8 to 12 mg/kg/day, with adjustments to achieve CsA trough levels as follows: Weeks 1 to 4, 250 to 400 ng/ml; Months 1 to 6, 200 to 350 ng/ml; Months 6 to 12, 100 to 300 ng/ml).

CsA whole-blood trough levels were determined using the monoclonal assay methods currently used at the investigational site by the local laboratory. Induction therapy was allowed according to local practice, and for induction sites, the reduction of CsA starting dose was allowed. The dose of EC-MPS used in this study was chosen to provide a systemic MPA exposure equal to that of an MMF dose (1,500 mg twice a day) indicated for the prophylaxis of organ rejection in heart transplantation. No MPA plasma levels were determined. The main exclusion criteria for this study were donor age >60 years, donor hearts with cold ischemia time of >6 hours or donors that had obvious coronary disease at time of transplant. Patients who were recipients of multiple solid-organ transplants, or who had received previous transplanted organs, were excluded. Endomyocardial biopsies were performed according to the usual local institutional protocol but were mandatory at Day 22 and at Months 3, 6 and 12. In addition, biopsies were performed at the discretion of the investigator. Approval was obtained from the ethics committee of each center, and informed consent was received from each patient before recruitment. The trial was performed in accordance with the Declaration of Helsinki.

The primary end-point of the study was to compare treatment failure in both groups, defined as the composite end-point of acute rejection, graft loss or death at 6 months. A post hoc analysis as recommended by trial investigators analyzed the incidence of biopsied and treated acute rejection episodes of at least International Society for Heart and Lung Transplantation (ISHLT), Grade 3a, acute rejection associated with hemodynamic compromise, graft loss, death or loss to follow-up (referred to as treatment failure II) at 6 and 12 months. Secondary objectives included treatment failure at 12 months as well as the gastrointestinal safety and tolerability of EC-MPS compared with MMF.

Moreover, in a sub-group of the total cohort, sequential pharmacokinetic (PK) assessments were performed at selected intervals (including Days 15 and 90). Only those patients with complete plasma concentration-time profiles (i.e., with all scheduled PK samples throughout the 12-hour dosage interval) were considered for PK evaluation of MPA. The exposure parameters (e.g., AUC and C_{max}) were normalized to EC-MPS 1,080 mg and MMF 1,500 mg, respectively.

Statistics

Efficacy was analyzed in the intent-to-treat (ITT) population and safety in the safety population. The primary

Download English Version:

<https://daneshyari.com/en/article/2973311>

Download Persian Version:

<https://daneshyari.com/article/2973311>

[Daneshyari.com](https://daneshyari.com)