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The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

BRIEF COMMUNICATION

Kinetics of generic tacrolimus in heart transplantation: A cautionary note

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KEYWORDS:
Immunosuppression;
tacrolimus;
rejection;
pharmacology

Tacrolimus is a core component of immunosuppressive regimens. This study compared active pharmaceutical ingredient (API) and dissolution kinetics of branded tacrolimus and formulations from three generic manufacturers (Mylan, Dr. Reddy's, Intas) including samples from patients who suffered acute cardiac allograft rejection. Generic samples showed similar API content compared to branded samples with no major impurities. Capsules that underwent uniformity testing had consistent capsule-to-capsule API. Dissolution testing showed similar profiles between branded tacrolimus and Mylan, but notable differences with Dr. Reddy's and Intas. The approximate maximal inhibitory concentration (IC_{50}) was highest in branded tacrolimus (29 minutes), followed by Mylan (26 minutes), Dr. Reddy's (19 minutes), and Intas (14 minutes) (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $p = 0.0199$, $F = 6.469$). This study suggests that the bioavailability of certain generic tacrolimus formulations peak significantly earlier than branded tacrolimus. Further study is needed to determine whether these differences are clinically relevant.
J Heart Lung Transplant 2021;40:569–572

Calcineurin inhibitors, primarily tacrolimus, are a core component of immunosuppressive regimens designed to prevent and treat rejection after solid organ transplantation, and are known to extend graft survival in heart transplant recipients.[1,2] Given the financial burden associated with immunosuppressive drugs, the development of bioequivalent generic formulations has been a welcome, albeit cautiously accepted alternative.[3,4] The use of generic tacrolimus and conversion from branded tacrolimus to generic formulations has been studied in the kidney transplant population and found to be generally safe with similar pharmacokinetics,[5,6] though the overall evidence is lacking.[7] There have also been reports in the pediatric kidney transplant population that recommend exercising caution when switching from a branded to generic formulation.[8] Although practitioners may specify "brand name" or a specific generic, pharmacy availability and insurer coverage allowances often determine use unless patients choose to spend out of pocket.

Immunosuppressive regimens have a narrow therapeutic index, and ineffective or inadequate treatment exposure has

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1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2021.03.009

dire consequences. Tacrolimus specifically requires therapeutic drug monitoring, and the pharmacokinetics of various generic preparations may vary within parameters specified and accepted by the Food and Drug Administration.[9] When evaluating possible generic substitutions, not only must active pharmaceutical ingredient (API) be considered, but drugs must be evaluated for excipients that may affect dissolution. It is possible for generic and branded medications to have the same API but different excipients that effect absorption, leading to variations in blood concentration and drug exposure.[10] The aim of this study was to test the consistency of API and dissolution rates in both branded tacrolimus and generic tacrolimus, including samples obtained from patients at a single institution who suffered acute cardiac allograft rejection in relationship to changing medication supplier.

The full methods can be found in the supplemental materials. Briefly, samples were obtained from different generic manufacturers (Mylan, Dr. Reddy's Laboratories, and Intas) and patients who suffered acute cardiac allograft rejection, and analyzed against branded samples (Astellas) and a pure tacrolimus standard. As indicated in Figure 1A (liquid chromatography- ultraviolet spectrophotometry (LC-UV)) and Figure 1B (liquid chromatography-mass spectroscopy (LC-MS)), samples from generic manufacturers showed a consistent number of peaks and retention time, indicating similar content of API compared to branded samples with no major impurities.

To test the uniformity of API, a sample of ten capsules from branded tacrolimus and a generic (Dr. Reddy's) tacrolimus were tested (supplementary Table 1). Both generic and branded samples had good capsule-to-capsule uniformity of API content. Furthermore, the API content in each capsule tested was slightly higher than expected, but similar to each other with the mean percent expected API in the generic tacrolimus 108.5% (SD 3.37, RSD 3.1) and in branded tacrolimus 105.6% (SD 2.32, RSD 2.2). The differences noted in LC-MS spectra may be the result of differences in excipient composition given the similar and consistent content of API.

A dissolution test was then performed. After 15 minutes, initial measurements showed similar dissolution between branded tacrolimus (Astellas) and generic drug manufactured by Mylan (26% ± 10% dissolved at 15 minutes), but notable differences in the percent tacrolimus dissolved between the branded and other two other generic samples (Figure 2A). Results of the full dissolution testing from 15 minutes to 150 minutes are shown in Figure 2B. The differences seen persisted throughout the test. At 30 minutes, generic Mylan samples were 58% ± 10% dissolved, similar to branded tacrolimus with 51% ± 17% dissolved. Generic drug manufactured by Dr. Reddy's and Intas were again

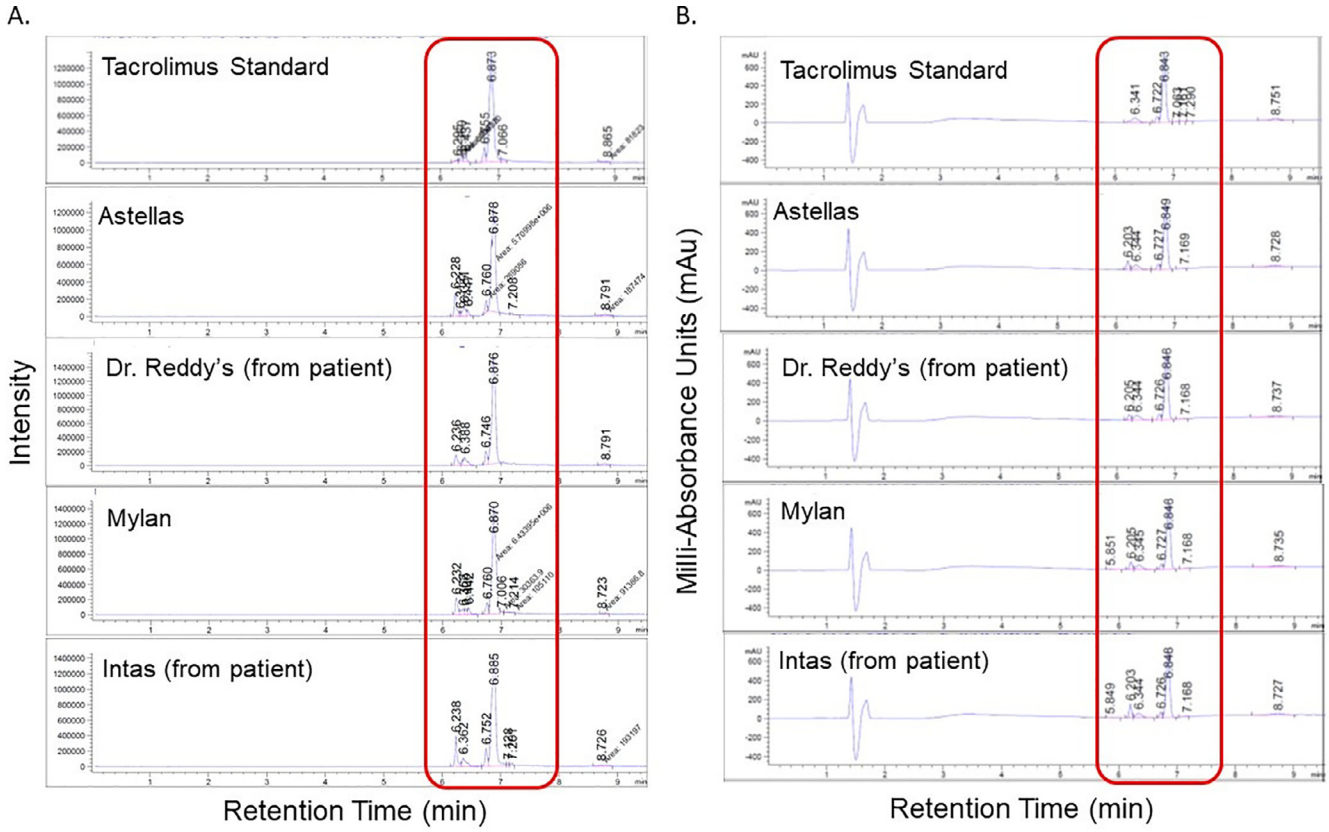

Figure 1 LC-UV spectra (A) and LC-MS spectra (B) of generic tacrolimus from Dr. Reddy's, Mylan, Intas, branded Astellas, and pure tacrolimus standard. Generic samples showed a consistent number of peaks and retention time, indicating similar content of API compared to branded samples.

(API, active pharmaceutical ingredient; LC-UV, liquid chromatography- ultraviolet spectrophotometry; LC-MS, liquid chromatography-mass spectroscopy).

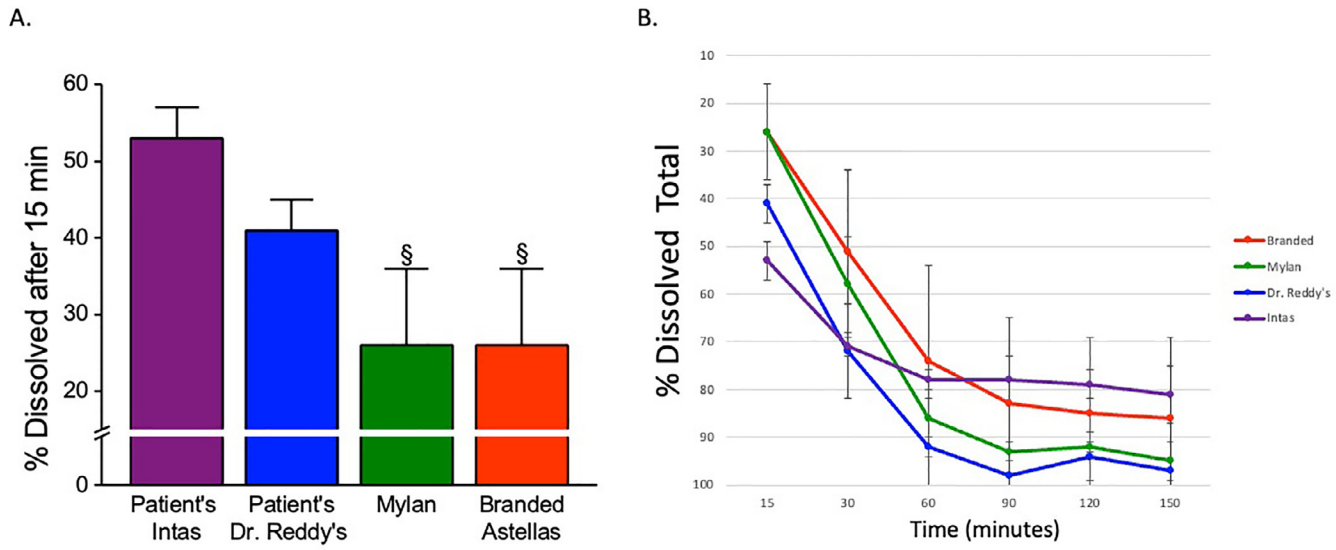

Figure 2 (A) Dissolution results from generic and branded tacrolimus after initial measurement (15 minutes). Statistical indicators: §p<0.05 versus patient's Intas (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $p = 0.0199$, $F = 6.469$). Values are mean ± SD (N = 2-3). (B) Dissolution results at 15, 30, 60, 90, 120, and 150 minute time points from generic and branded tacrolimus capsules. Results shown as percent dissolved. (ANOVA: analysis of variance, SD: standard deviation).

notably more dissolved at this time interval at 72% ± 10% and 71% ± 2%, respectively. From 60 to 150 minutes, the branded samples as well as the three generic manufacturer samples were relatively consistent with each other, though the percent dissolved still varied between different manufacturers.

Finally, the approximate maximal inhibitory concentration (IC_{50}) for each sample was measured (Figure 3). Branded tacrolimus had the highest IC_{50} at 29 minutes, followed by generic drug from Mylan with an IC_{50} of 26 minutes, then generic drug manufactured by Dr. Reddy's (obtained from a patient with acute rejection) at 19 minutes, and finally generic drug manufactured by Intas (obtained from a patient with acute rejection) at 14 minutes ($p < 0.05$ versus patient's Intas (Student-Newman-Keuls Multiple Comparisons Test; overall ANOVA: $p = 0.0199$, $F = 6.469$) which suggests that the potency of the generic medications obtained from patients who suffered acute rejection peaked significantly earlier than branded tacrolimus or generic tacrolimus manufactured by Mylan.

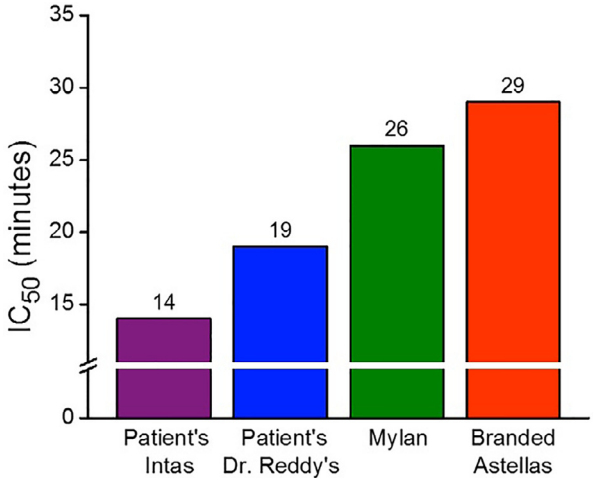

Figure 3 Approximate IC_{50} (in minutes) of dissolution from generic and branded tacrolimus capsules.
(Abbreviations: IC_{50}: maximal inhibitory concentration)

The results of this study show that, although API content was similar amongst the branded and generic tacrolimus preparations tested, there was marked variance in the dissolution rates of drugs between manufacturers. Branded tacrolimus from Astellas and generic tacrolimus from Mylan had similar kinetics of drug release, while samples from Dr. Reddy's and samples from Intas (obtained from patients who suffered acute cardiac rejection) had a much quicker dissolution, in some cases nearly twice the release rate. There is concern that these observed differences in release could affect in-vivo absorption, and subsequently affect therapeutic efficacy. We suspect these differences can be attributed to excipient compounds in each formulation that influence the dissolution process.

Our study has several limitations, including a limited number of samples and lots from a small group of manufacturers that were tested from a single center. While instances of acute rejection can be caused by multiple and complex interactions in post-transplant care, given that the therapeutic window of immunosuppression is narrow, small alterations to either the API or dissolution profile can potentially lead to serious adverse outcomes. This descriptive analysis prompts the need for continued investigation into additional lots of both generic and branded tacrolimus to characterize differences in dissolution rates and consistency of API. Further study is needed to determine whether these differences in the kinetics of various generic tacrolimus formulations may be associated with worse clinical outcomes. We urge transplant professionals to be mindful of the potential limitations of changing the supply source of generic immunosuppressive medications and to consider this variable as an

important arbiter when unexpected rejection is encountered without an obvious cause.

Financial conflicts of interest

Dr. Mehra reports personal fees from Abbott, Medtronic, Janssesn, Mesoblast, Baim Institute for Clinical Research, Portola, Bayer, Triple Gene, NupulseCV, Leviticus, and FineHeart outside the submitted work. All other authors have no disclosures.

Author contributions

Each author has participated sufficiently in the work to take public responsibility for the content. ZJI, RCS (study design, data analysis, writing of manuscript), HL (study design, writing of manuscript), JBW, SSCRS, RPM (data analysis, writing of manuscript), EMH, MRM (writing of manuscript).

Acknowledgements

We thank Dr. Joseph G. Rogers for his insightful contributions to this work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.03.009.

Supplementary data

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