

Generic Immunosuppressants in Transplantation

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# Commentary on the recommendations of the European Society for Organ Transplantation Advisory Committee on generic substitution of immunosuppressive drugs

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In 2010, the Council of the European Society for Organ Transplantation formed an Advisory Committee to formulate recommendations on the use of generic drugs in solid organ transplant recipients. The initiative was taken as a result of concerns regarding generic substitution of immunosuppressive drugs. The recommendations were published in *Transplant International*, and this paper is a short summary of its contents.

**Keywords:** Ciclosporin, generics substitution, immunosuppression, mycophenolate, tacrolimus, transplantation

## Introduction

Solid organ transplant recipients are treated with immunosuppressive drugs in order to prevent rejection of their grafts. The most frequently used maintenance immunosuppressive drugs in Europe are the calcineurin inhibitors (tacrolimus and ciclosporin), and mycophenolic acid (mycophenolate mofetil). For all three drugs patents have expired and generic formulations have been registered. In 2010, the Council of the European Society for Organ Transplantation (ESOT) formed an Advisory Committee to formulate recommendations on the use of generic drugs in solid organ transplant recipients [1]. The initiative was taken as a result of concerns regarding generic substitution of immunosuppressive drugs. Health insurance companies encourage the prescription of generic drugs, as they have substantially lower prices compared to the original brand-name product. In some

countries this led to substitutions by pharmacists, even in patients who had a prescription for a brand name drug. Prescribers felt that they were no longer in control of what drug their patients were taking. Uncontrolled substitutions by pharmacists have been linked to graft dysfunction, and the transplant community approached ESOT, and national transplant societies, which mobilized working groups and advisory committees to formulate guidelines on how to deal with generics substitution [2]. In this paper, the contents of the ESOT guidelines are summarized, as well as some recent developments in this field. For the full text the reader is referred to the original publication [1].

## Bioequivalence and generic drugs

Registration of generic drugs largely depends on the demonstration of bioequivalence. The readers of *GaBi Journal* are very



familiar with the design and interpretation of bioequivalence studies, and this will not be further discussed. There are subtle differences in regulatory requirements for bioequivalence between the American (FDA – Food and Drug Administration) and European (EMA – European Medicines Agency) agencies, but by and large the procedures are similar. An important difference however is that in 2010, for narrow therapeutic index drugs, EMA narrowed the 90% confidence interval of the ratio between the average rate and extent of bioavailability of the test formulation and the reference formulation from an interval of 80–125% to an interval of 90–111%, while FDA is still applying the wider interval. For the calcineurin inhibitors the stricter criteria are being applied by EMA, but for mycophenolate mofetil the wider range is still being used, as this drug is not considered to be a narrow therapeutic index drug.

## Patients or healthy volunteers

Bioequivalence studies are generally performed in healthy human volunteers with normal renal, hepatic and cardiac function. The results of these studies are extrapolated to transplant populations. Although the smaller between-patient variability in healthy volunteers is an advantage in the detection of small differences in drug bioavailability between different formulations, many transplant physicians would favour bioequivalence studies in the respective patient populations. Some pharmaceutical companies have indeed performed such studies in transplanted patients, not as a regulatory requirement, but to convince prescribers that the generic drug is also bioequivalent to the reference product in their patients. It would offer such companies a marketing advantage, and prescribers would feel more comfortable in prescribing these formulations.

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Submitted: 27 March 2013; Revised: 5 May 2013; Accepted: 13 May 2013; Published online first: 20 May 2013

## AUC and $C_{max}$

The maximum observed drug concentration ( $C_{max}$ ) and the area under the curve (AUC) are the two parameters used to decide on bioequivalence. In daily practice, however, the immunosuppressive drugs are monitored by measurement of the pre-dose concentration ( $C_0$ ), although some argue that drug concentration measurements at other time points would be more appropriate [3]. Whether or not the correlation between the pre-dose concentration and AUC is the same for generic and reference drug product is not tested. Nevertheless, the same target concentrations for both products are strived for, although prescribers perceive this situation as a lack of evidence. In the ESOT guidelines there is a plea to investigate the relationship between the measured surrogate pharmacokinetic parameter, e.g.  $C_0$ , or  $C_2$ , and exposure (expressed as AUC) for the respective formulations. When such data are available, regular drug monitoring can be performed under valid assumptions.

## Generic to generic substitution

Regulators claim that based on the demonstration of bioequivalence, the reference drug product and the generic formulation are fully interchangeable [4]. However, following a first substitution from the reference drug product to a generic formulation, subsequent substitutions from one generic drug to another often follow. It is important to realize that generic formulations are not necessarily bioequivalent amongst themselves. Although all generic formulations have been tested against the reference drug product, there is no requirement that generic formulations show bioequivalence with generic formulations that have been registered already. Knowing that the acceptance criteria allow for a difference between reference drug product and generic of 20%, it is theoretically possible that substitution from one generic drug to another leads to a substantial deviation in drug exposure. In the ESOT guidelines this omission in the registration process of generic formulations is highlighted.

## Uncontrolled substitutions

When the prescriber has specified a particular brand-name drug and the dispensing pharmacist intends to give the patient something else, both prescriber and patient should be informed and both prescriber and patient should agree. Only then can the prescriber ask the patient to return to the clinic at a shorter time interval, to check drug concentrations and to ensure that the patient is taking the right drug in the right dose. Unfortunately, the prescriber is not always informed, and a reliable system to systematically notify the prescriber of a change in the dispensed formulation is not available. The ESOT guidelines warn of uncontrolled substitutions and recommend that pharmacists contact prescribers before dispensing alternative formulations.

## Confused patients

Although brand-name drugs and generic drugs may be interchangeable with respect to their drug exposure and their clinical effects, they can differ substantially in their appearance. Consumers of generic drugs must be prepared to receive pills of a different size, colour, and shape, depending on which manufacturer is supplying their pharmacies. With numerous generic to generic substitutions over a period of time, patients may get confused and make mistakes. Such mistakes may have serious consequences [5]. The ESOT guidelines ask for a system of more uniform drug appearance in order to reduce medical error and promote patient adherence to treatment regimens that involve generic drugs [6].

## Conclusion

Immunosuppressive drugs are expensive and life-long immunosuppressive therapy of transplant patients is associated with high financial costs. ESOT is not opposed to the use of generic drugs. ESOT Advisory Committee stressed that savings in the cost of immunosuppressive drugs will benefit health care and society, as long as the overall cost is not increased due to additional patient care and drug monitoring.

Uncontrolled substitutions and repetitive substitutions from one generic drug to another should be avoided. The guidelines attempt to regulate the process of generic substitution of immunosuppressive drugs in transplant recipients. This is a vulnerable patient population. The demonstration of bioequivalence is not sufficient to conclude there is unconditional interchangeability [7].

**Competing interests:** Professor Teun van Gelder has received honoraria, research grants or lecture fees from Astellas, Pfizer, Roche, Sandoz and Wyeth; and is a member of the Dutch Novartis Transplant Advisory Board.

**Provenance and peer review:** Commissioned; externally peer reviewed.

## References

1. van Gelder T; ESOT Advisory Committee on Generic Substitution. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. *Transpl Int*. 2011 Dec;24(12):1135-41.
2. Harrison JJ, Schiff JR, Coursol CJ, Daley CJ, Dipchand AI, Heywood NM, et al. Generic immunosuppression in solid organ transplantation: a Canadian perspective. *Transplantation*. 2012 Apr 15;93(7):657-65.
3. Knight SR, Morris PJ. The clinical benefits of cyclosporine C2-level monitoring: a systematic review. *Transplantation*. 2007 Jun 27;83(12):1525-35.
4. Maliepaard M, et al. Equivalence of generic medicines in general and immunosuppressants in particular – a regulatory opinion on switching of cyclosporin, tacrolimus and mycophenolate mofetil. *Generics and Biosimilars Initiative Journal (GaBi Journal)*. 2013;2(2):86-90. doi:10.5639/gabij.2013.0202.019
5. Greene JA. The substance of the brand. *Lancet*. 2011 Jul 9;378(9786):120-1.
6. Greene JA, Kesselheim AS. Why do the same drugs look different? Pills, trade dress, and public health. *N Engl J Med*. 2011 Jul 7;365(1):83-9.
7. Van Gelder, T. Why bioequivalence and unconditional interchangeability of generic drugs are not the same. *Generics and Biosimilars Initiative Journal (GaBi Journal)*. 2013;2(2):83-5. doi:10.5639/gabij.2013.0202.020  
DOI: 10.5639/gabij.2013.0203.031

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