PERSPECTIVE

Generic Immunosuppressants in Transplantation

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Equivalence of generic medicines in general and immunosuppressants in particular – a regulatory opinion on switching of ciclosporin, tacrolimus and mycophenolate mofetil

Marc Maliepaard[1], PhD; Yang Yu[1,2], PharmD; Professor Hubert GM Leufkens[1,3], PharmD, PhD

This position paper deals with our regulatory opinion on registered generic immunosuppressants such as ciclosporin, tacrolimus and mycophenolate mofetil, and provides arguments why these medicines are considered equally safe and effective as the branded drug based on demonstrated bioequivalence. Though regulators acknowledge the worries from the field, we are of the opinion that there are no compelling pharmacological arguments to date against the sensible use of generic immunosuppressants in clinical practice, under the shared and mutual care by prescribers and pharmacists.

Keywords: Bioequivalence, drug safety, generic, immunosuppression, regulation

Background

As soon as the protection period of 10 years of a branded drug has expired, it is possible to seek a marketing authorization for a generic form of this drug. This gives rise to the situation that patients may no longer be treated with the original product (proprietary, branded drug), but with a generic medicine. In that case generic substitution takes place, where the branded drug is exchanged with a product with an identical active ingredient. In the last 30 years we have gained extensive experience with such generics substitution, not only in The Netherlands but also in other parts of Europe and the US. For example, in The Netherlands, treatment with generics has now become the standard for drugs such as statins, proton pump inhibitors and antihypertensive drugs.

Though the Dutch Medicines Evaluation Board (*College ter Beoordeling van Geneesmiddelen*, MEB) is not directly involved in the actual substitution strategy in The Netherlands, registration of generic medicines will only take place if the MEB is convinced that the generic medicine has the same efficacy and safety profile as the innovator medicine. As our contribution to the discussion on generics substitution, we explain why the MEB considers this to be the case also for immunosuppressants, based on the quality of the medicine and bioequivalence testing.

Generic facts

What are the facts on generic medicines? A generic medicine is a product with the same active ingredient, the same strength and the same pharmaceutical form as the branded drug (in other words, is *pharmaceutically equivalent*). If the manufacturer of the generic drug product demonstrates that its exposure in time (which, for products with immediate release characteristics, is determined by area under the curve (AUC) and C_{max}) is equal to that of the branded medicine – so the two products are bioequivalent – the generic and branded medicines are considered to be *therapeutically equivalent*. This assumption is logical, because when a drug is absorbed in the same way (as demonstrated by the bioequivalence study), its further pharmacological behaviour only depends on the characteristics of the molecular active ingredient. The potential differences in inactive excipients between branded and generic drug formulation are then no longer relevant. For generic and branded drugs, the molecular active substance is qualitatively and quantitatively the same. Therefore, once bioequivalence is demonstrated, the company that manufactures the generic drug can refer to the clinical studies performed with the branded drug for the efficacy and safety of the generic drug product, with no need for additional clinical trials prior to registration.

In most cases, bioequivalence is demonstrated in healthy volunteers [1]. It is well known that the exposure in healthy volunteers may be different than that in patients, due to comorbities of the patient. However, it is important to realize that this will affect branded and generic medicines equally. In addition, the actual exposure in a healthy volunteer is the result of a combination of endogenous factors, including renal and hepatic function, metabolizer status, e.g. poor or extensive metabolizer; ethnic background, and gastric pH, which affect a drug's absorption, metabolism and elimination. When comparable exposure between a branded and generic medicine has been demonstrated in a healthy volunteer, relative exposure in patients, determined by a different mix of these endogenous characteristics, also is expected to yield comparable exposure. Versantvoort et al. [2] illustrated this principle with a bioequivalence study in which a poor metabolizer was present among extensive metabolizers: though the exposure in the poor metabolizer was dramatically higher – probably even requiring

Author for correspondence: Marc Maliepaard, PhD, Senior Clinical Assessor, Clinical Pharmacologist, Pharmacotherapeutic Group 3, College ter Beoordeling van Geneesmiddelen/Dutch Medicines Evaluation Board, PO Box 8275, NL-3503 RG Utrecht, The Netherlands

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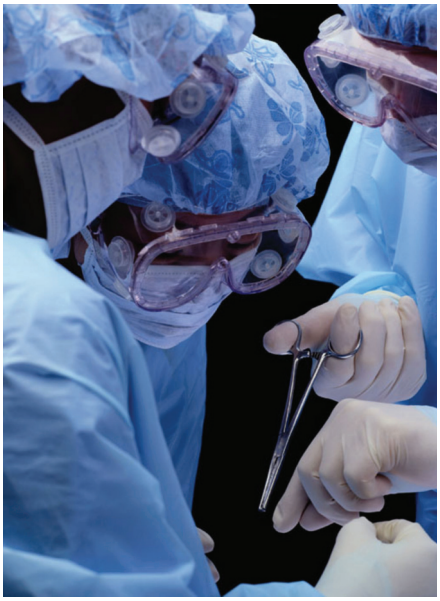

a dose adjustment in clinical practice – the relative exposure of the branded and generic drug within this subject remained comparable. The same principle will hold for other comorbidities, like renal or hepatic impairment: when bioequivalence has been demonstrated in healthy volunteers, the relative exposure change will be the same for the branded and generic medicine. Therefore, bioequivalence demonstrated in healthy volunteers will be valid for the patient population.

In most cases, excipients are inactive, and a single-dose bioequivalence study is considered sufficient to obtain registration of a generic drug. If active excipients, such as in a gastro-resistant coating, are present in the drug formulation, additional data specifically relevant to this active excipient are required in order to demonstrate that the excipient's behaviour is comparable with that of the branded medicine. For example, in case of a gastro-resistant coating, comparable pH dependent dissolution should be demonstrated, and an additional bioequivalence study with food (resulting in increased gastric pH) should be provided [3]. For other specific formulations, e.g. liposomal, sorbitol, cyclodextrin or microemulsion containing formulations, other specific additional requirements are needed [3, 4].

Of note, bioequivalence studies are not only used for registration of generic medicines, but also in drug development of a newly invented medicine where appropriate [5], or a line extension after registration of a branded medicine. For instance, registration of the 0.5 mg Prograf strength was based on a bioequivalence study under single-dose conditions [6]. It is therefore clear that identical regulations are used both for branded and generic drug products, and thus, these medicines undergo the same rigorous scrutiny upon admission.

Normally, bioequivalence is considered to have been demonstrated when the 90% confidence intervals of the generic:branded ratios for AUC as well as C_{max} are within 80–125%. These acceptance criteria are strict, and are outlined in the Guideline on the Investigation of Bioequivalence [1]. Additional stringent requirements are placed on the actual analytical assay that is used in such bioequivalence studies to quantify the plasma or blood concentrations [7]. With respect to generic immunosuppressants, additional care has been taken by the regulatory authorities, by narrowing the acceptance range for some immunosuppressants, in order to further reduce the likelihood of obtaining clinically relevant differences in exposure when switching to and from generic medicines. The option to narrow the acceptance range is given in the current (2010) as well as the previous version (2001) of the Guideline on the Investigation of Bioequivalence, for medicines with a narrow therapeutic index (NTI). Since a worldwide definition of an NTI is lacking, this is considered by the European Medicines Agency (EMA) on a case-by-case basis. Indeed, the acceptance criteria for generic immunosuppressants have been adjusted, i.e. to 90–111% for ciclosporin AUC and C_{max}, and to 90–111% and 80–125% for tacrolimus AUC and C_{max}, respectively [3]. Due to the microemulsion formulation applied in Neoral, which has led to a pronounced increase in predictability of the ciclosporin exposure and reduced food effect as compared to its precursor Sandimmune, bioequivalence for ciclosporin generics should be demonstrated under fasted as well as fed conditions. With regard to tacrolimus, only the 90% confidence intervals for AUC was narrowed, since due to accumulation of tacrolimus upon repeated dosing, a potential difference between formulations in C_{max} after single dosing can be expected to be less at steady state, if AUC is the same for the two formulations. Therefore, the normal acceptance criteria for C_{max} can be used in single-dose bioequivalence studies for tacrolimus [3]. For mycophenolate mofetil, for which bioequivalence is demonstrated based on exposure of the mycophenolic acid metabolite, no narrowing of the criteria was considered necessary by EMA [3].

Overall, the strict requirements for demonstrating bioequivalence are equally valid for branded and generic drug products. Thus, the demonstration of bioequivalence is strong evidence to secure the substitution of a generic product for the branded medicine.

Generic doubts

Nevertheless, questions arise from a number of clinical disciplines that, due to claimed specific characteristics within their patient population, some patients are not suitable for generics substitution. One of these disciplines is transplantation medicine. Concerns regarding the substitution of immunosuppressants by generic drug products are understandable from the recipient's perspective: the impact of failing immunosuppressant therapy following transplantation can be dramatic. In the scientific literature, some publications support generics substitution, e.g. by suggesting comparable efficacy and safety with ciclosporin generic formulations as with branded equivalents [8-12]. Similar support comes from demonstrations of bioequivalence of generic and branded tacrolimus in kidney transplant patients [13] and comparable clinical outcomes with branded or generic tacrolimus in kidney and liver transplant patients [14, 15], with the routinely applied therapeutic dose monitoring for tacrolimus being advised as a safeguard [16, 17]. Conversely, over the past few years, a number of reviews and clinical guidelines raise concerns about generics substitution [18, 19]. In Europe, the European Society for Organ Transplantation (ESOT) published recommendations on generics substitution of immunosuppressive drugs, which were based on the guideline drafted by the Dutch Renal Transplant Society [18]. Although some concerns in ESOT recommendations are acknowledged, overall, in our opinion there appears to be an overemphasis on assumed shortages of pharmacokinetic (PK) or clinical data relating to generic drug product registration. Examples of such assumptions include those relating to the C_{trough}/C_{min}, multiple dose conditions, or the fact that bioequivalence between different generics is not formally tested. These topics are discussed below. Although the requirements

posed by the regulatory authorities on the description of PK of generics are limited (i.e. almost equal AUC and C_{max}, and similar quality), these requirements are well thought over. Many of the concerns raised regarding generics substitution are not deducible to scientific facts or studies, but often involve a number of recurring arguments which are demonstrably incorrect. We discuss a number of those related to immunosuppressants below.

One incorrect assumption often expressed is that, though AUC and C_{max} obtained with a branded immunosuppressive drug and its generic may be the same, there may still be differences in certain critical points of the plasma concentration–time curves. This argument has been expressed for ciclosporin, where plasma concentrations two hours after administration (C_2) or trough levels (C_{trough}) are used to monitor and adjust ciclosporin exposure and dose [18]. However, for an immediate-release product like ciclosporin the PK after the initial absorption from the gastrointestinal tract is essentially governed by the molecular active substance only. Since this substance is identical for the branded and generic ciclosporin formulations, differences in C_2 or C_{trough}, despite comparable AUC and C_{max} in the case of demonstrated bioequivalence, will be an extremely unlikely event. In a field that is so familiar with therapeutic drug monitoring, it is remarkable that this is seen as a possibility.

Another argument raised is that bioequivalence for immunosuppressants should be demonstrated under steady-state conditions instead of the currently required single-dose conditions only, since in clinical practice steady-state conditions may be more important [18]. It is agreed that in clinical practice steady-state conditions are important, and it is acknowledged that for certain medicinal products the absolute exposure under steady-state may be different from that after a single dose, due to accumulation upon multiple dose administration. However, there is no reason to assume that the relative exposure obtained under single-dose conditions will be different from that under steady-state conditions. It is well known that the sensitivity of detecting a difference in exposure between two different formulations under steady-state conditions is less than after a single dose [1]. Viewed from the opposite perspective, assessment of bioequivalence under steady-state conditions for ciclosporin would lead to a less stringent assessment of bioequivalence. Applying lower standards for generics is certainly not acceptable to authorities as the Dutch MEB and EMA. After absorption of a medicinal product, its PK is only determined by the molecular active substance. Therefore, there is no reason to assume that the PK behaviour will be different for an immediate-release generic drug product compared with the branded drug under steady-state conditions, when a comparable absorption has been demonstrated under the most sensitive condition, i.e., after single-dose administration.

In certain cases, therapeutic substitution (the exchange of two different types of formulations or two different active ingredients for the same indication) appears to be used to indicate that presumed problems with generics substitution are plausible [18]. This is exemplified by the reported reference to the product description (Summary of Product Characteristics, SmPC) of tacrolimus formulations, which contain a warning that patients must remain on the same formulation. This warning makes sense, and it is clear that the underlying reason for this warning is the fact that there are different types of branded tacrolimus formulations with different release characteristics and therefore different pharmacokinetics on the market, namely Prograf, being an immediate release formulation given twice daily and Advagraf, a prolonged release formulation for once daily administration. Everyone would agree that these different formulations, which are intended for either once daily or BID (twice a day) dosing, should not be interchanged, and indeed issues upon accidentally interchanging these two branded tacrolimus formulations have been reported. However, it is unjust to extrapolate founded warnings in the tacrolimus SmPC against substitution between different types of tacrolimus formulations to substitution between equivalent types of tacrolimus formulations, as in the case of generics substitution, where the release characteristics are equivalent.

The suspicion that generic–generic substitution leads to increased, potentially clinically relevant variability in exposure, which is also used as an argument against generics substitution [18], has not been demonstrated. The occurrence of greater, possibly clinically significant, differences in exposure is a theoretical possibility, which would occur when 90% confidence intervals of different generics would be in the opposite part of the 80–125% criterion. However, given the small observed difference in mean exposure between an arbitrary generic and branded drug [20], the occurrence of great differences in exposure upon generic–generic substitution seems unlikely, though formally it cannot be excluded. For the antiepileptic drugs gabapentin and topiramate, which are registered in The Netherlands, the absence of increased differences in exposure when different generics were exchanged was shown by research conducted at the MEB using bioequivalence data obtained from registration files at the MEB. These data were used to estimate 90% confidence intervals following the substitution of different generic formulations of gabapentin or topiramate [21]. Research towards such simulated generic–generic substitution data for immunosuppressants is currently ongoing at the MEB. In that respect, it is important to note that ciclosporin generics in The Netherlands were registered prior to the narrowed acceptance criteria of 90–111% for this product, both under fasting and fed conditions, implemented by EMA. MEB closely monitors any signs of unacceptable efficacy or safety reports related to these drugs.

Despite the arguments provided above, it cannot be disputed that in certain isolated cases, issues with generics are reported. However, these are considered as exceptional cases, e.g. sometimes related to intolerance to certain excipients like lactose, fructose or galactose, which may be present in generics and not in branded products (and vice versa). However, in the vast majority of switches, substitution proceeds without problems. It is acknowledged that factors other than differences in exposure may play a role in the perception of generics and the outcome of generics substitution in patients, for example, with differences in shape and colour of generics, which may lead to distrust, mistakes or reduced compliance among patients. The consequences of such differences may even increase when the branded and generic drug are frequently changed, which is a realistic scenario in The Netherlands, where the frequency of switching has increased over the years due to the current pricing and reimbursement policy of the Dutch health insurance

companies. Frequent switching to other generics may be expected to negatively affect compliance and confidence, could potentially increase the chance of errors, and should therefore be avoided as much as possible.

It is the joint responsibility of the pharmacist and prescriber to monitor this switching and to provide satisfactory communication for the benefit of the patient, in case generics substitution takes place. In our opinion, inadequate communication between pharmacist and prescriber cannot be used as an argument against the use of generics [18], but should better lead to incentives to solve this issue.

Uncertainty about the underlying principles and legislation of generics, combined with otherwise well appreciated and valued patient care, appear to be leading in the frequently provided arguments against generics substitution, rather than solid evidence for the occurrence of problems. It is reasonable to assume that a well-informed prescriber is able to play a major role in the perception of generic immunosuppressants by the patient, and in that respect, MEB should also take a part in this discussion and education.

Regulatory agencies like MEB are actively involved in governing the safe use of generic immunosuppressants. Pharmacovigilance structures are in place, and adverse events reported related to immunosuppressants, as well as other medicinal products, are taken very seriously. In case there are signs of unexpected disproportional adverse events or inefficacy with any drug – be it a generic or branded – MEB is obliged to take action. For the pharmacovigilance system to work, it is essential to report issues to the relevant pharmacovigilance centres in the different EU Member States, in order to be able to keep a close eye on the actual quality of generics, and to reduce the time before a signal can be picked up. In that sense, regulations have recently been amended with a more pronounced place for reporting adverse events by patients, who are considered 'hands-on' experts.

Conclusion

From a regulatory point of view, generic immunosuppressants like ciclosporin, tacrolimus and mycophenolate mofetil are considered as safe and effective as the branded drug based on demonstrated bioequivalence, and therefore considered interchangeable. Though we are aware of worries expressed in the field, we are of the opinion that there are no compelling pharmacological arguments to date against the sensible use of generic immunosuppressants in clinical practice, under the shared and mutual care of prescribers and pharmacists.

For Patients

Generic drugs are prescribed more and more. Sometimes, the change of prescription from branded to a generic medicine leads to unrest and doubts among patients, e.g. on whether generic drugs are equally safe and work equally well as the branded medicines. These doubts are acknowledged and understood. In this paper, we aim to clarify what is done by regulators to safeguard the use of generics as much as possible. From the prescriber's and pharmacist's perspectives, we expect and promote a professional and adequate collaboration to take appropriate action in isolated cases when a generic drug does not meet its expectation in an individual patient.

Editor's comments

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Disclaimer

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Authors

Marc Maliepaard[1], PhD
Yang Yu[1,2], PharmD
Professor Hubert GM Leufkens[1,3], PharmD, PhD

[1]Dutch Medicines Evaluation Board, Utrecht, The Netherlands
[2]Department of Pharmacology, Maastricht University Medical Centre, Maastricht, The Netherlands
[3]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands

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