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Advisory Committee Recommendations on Generic Substitution of Immunosuppressive Drugs

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(on behalf of the ESOT Advisory Committee on Generic Substitution)

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Conflicts of interest

Dr. Anders Asberg has received research grants and lecture fees from Roche.
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Dr. Dario Cattaneo has received travel grants from Roche and MSD.
Dr. Chris Dudley has reported no conflicts of interest.
Dr. Magedalena Durlik, has reported consultancy fees from Roche, Novartis and BMS, and lecture fees from Roche, Novartis, Teva, Genzyme, Apotex and Valeant.
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Dr. Anders Hartmann has received a research grant from Roche, and lecture fees from Novartis and Amgen.
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Dr. Iain MacPhee has received research grants from: Astellas, Novartis, Roche and Wyeth(now Pfizer), lecture fees from: Astellas, Novartis, Roche, and attended Advisory Boards or consulted for: Astellas, Britol Myers-Squib, Novartis, Roche, Teva, Wyeth (nowPfizer).
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Dr. Daniel Serón has received research grants from Astellas and lecture fees from Novartis,Astellas, Roche and Bristol Myers Squibb.
Dr. Teun van Gelder has received research grants or lecture fees from Roche, Astellas and Wyeth, and is a member of the Novartis Transplant Advisory Board.

Introduction

Solid organ transplant recipients are treated with immunosuppressive drugs to prevent rejection of their grafts. The most frequently used maintenance immunosuppressive drugs in Europe are calcineurin inhibitors, mycophenolic acid and to a lesser extend mTOR-inhibitors (or Proliferation Signal Inhibitors: PSI). For a number of these compounds drug patents have expired in 2009 and 2010 and generic formulations have recently entered the market. There is considerable debate regarding the efficacy and safety of generic drug substitution in solid organ recipients.

In November 2010 the Council of ESOT has commissioned an Advisory Committee to formulate recommendations on the use of generic drugs in solid organ transplant recipients. This initiative was taken to highlight regulatory and clinical concerns regarding generic substitution of immunosuppressive drugs. In this report the Advisory Committee recommendations to the Council of ESOT are summarized.

Executive summary

Switching transplanted patients who require lifelong immunosuppressive therapy from brand name immunosuppressive drugs to generic formulations can lead to significant lower drug costs. In the registration process of generic narrow therapeutic index drugs (NTIDs) the authorities have recently issued guidelines for demonstrating bioequivalence based on stricter criteria than those currently used for other drugs. Although these stricter criteria represent an important improvement it remains surprising that different generic drug formulations do not require demonstration of bioequivalence amongst themselves, although substitution between these formulations is permitted and hence likely to occur.

As a society ESOT is not opposed to the use of generic drugs. However, to safeguard the substitution process of generic drugs, we propose to regulate generic substitution of the NTIDs in our vulnerable patient populations. This applies to the calcineurin inhibitors (cyclosporin and tacrolimus), mTOR inhibitors (sirolimus and everolimus) and to the mycophenolates (mycophenolate mofetil and mycophenolate sodium). To achieve safe and controlled generic substitution we propose the following guidelines:

1 Switching between the brand name drug and a generic formulation, and also between different generic formulations should be initiated only by the transplant physician (in this report with this term we refer to a practitioner specialized in transplantation medicine, either a transplant physician or a transplant surgeon).

2 Each switch needs to be followed closely to assure that the correct therapeutic window is established.

3 Repetitive consecutive substitutions to other generic formulations of the same drug should be avoided. To ensure this, it is recommended that the transplant physician when prescribing uses a specific brand name generic formulation.

4 Patients should be informed about generic substitution, they should be educated how to identify the different formulations of the same drug, and they should alert the transplant physician if uncontrolled substitutions are made.

5 New generic formulations of immunosuppressive drugs that do not fulfil the stricter bioequivalence criteria should not be used. Similarly, the use of already marketed generic immunosuppressants should be discouraged unless they prove to be bioequivalent according to the recently updated EMA guidelines.

6 Further research is needed to fully explore the benefits and limitations of generic drug substitutions.

7 (In case of future substitution of biological to biosimilar immunosuppressive drugs, clinical bioequivalence criteria should be carefully formulated, e.g. Belatacept, Campath).

Bioequivalence and generic drugs

Drug patents enable pharmaceutical companies to exclusively market newly developed compounds for an arbitrary restricted time period. Patent lifetime differs between countries and renewal of an expired patent is normally not possible. After expiration of a drug patent the monopoly marketing position of the original patent holder is void. Other companies will then be allowed to enter the market with generic versions of the same active ingredient, which typically leads to strong competition and to substantially lower prices for both the original brand name product and the generic forms [1].

Generic drugs are registered based on bioequivalence. Two medicinal products containing the same active substance are considered bioequivalent if their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.[1] In bioequivalence studies, the plasma concentration time curve is used to assess the rate and extent of absorption. The pharmacokinetic parameters AUC (the area under the concentration time curve) and Cmax (the maximum plasma concentration) are used to decide on bioequivalence of the tested products. For the logarithm of these parameters the 90% confidence interval for the ratio of

[1]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003011.pdf

the test and reference product should be contained within the acceptance interval of 80–125%.[2] In the recently updated EMA guidelines it is stated that ''additional pharmacokinetic parameters should be determined and reported in particular conditions.'' These parameters include, beside AUC and Cmax, also the terminal rate constant, the half-life and the Tmax. The latter parameter is of particular relevance for immunosuppressive agents (think about the ''story'' of C2 proposed as surrogate of Cmax or think to the application of limited sampling strategies based on given sampling times used to predict AUC). Accordingly, bioequivalence studies for generic immunosuppressants should deal also with Tmax, half-life and trough (see below).

Although for most drugs the interval between 80% and 125% was considered appropriate, in recent years there have been discussions regarding the validity of this target interval for products with a narrow therapeutic index. For the purpose of bioequivalence requirements, narrow therapeutic index drugs (NTIDs) are considered to be those compounds for which there is a risk of clinically relevant differences in efficacy or safety between two products even when the conventional criteria for bioequivalence are met. NTIDs often have steep concentration response relationships for efficacy, toxicity, or both. Dosing generally needs to be individualized based on blood/plasma concentration monitoring and there may be potentially serious clinical consequences in the event of concentrations outside the therapeutic window. Remarkably, the registration authorities have not been able to define a set of criteria to categorize drugs as either NTIDs or not and a judgment must be made in each individual case. Several immunosuppressive drugs are considered to be examples of NTIDs. In 2010 the European Medicines Agency has recommended that in cases where the acceptance interval needs to be tightened, the acceptance interval for concluding bioequivalence should be narrowed to 90–111%.[3]

Bioequivalence studies are generally performed in healthy human volunteers with normal renal, hepatic and cardiac function and on no other medications. This potential limitation of the bioequivalence studies with the assumption of extrapolation to transplant populations should be recognized. Another important limitation of actual (and previous) bioequivalence studies refers to ''steady state'' conditions. In fact, 90% of bioequivalence studies are carried out using single drug dose. Again, a situation really far from the clinical day-to-day practice. Multiple dosing studies are important also to verify the bioequivalence of trough drug concentrations (that are the pharmacokinetic tools used in the routine management of transplant patients).

Generic substitution[4]

If a generic drug is shown to be bioequivalent with a brand name drug it is assumed that they will also be therapeutically equivalent. Unlike the approval criteria for innovator products, requiring manufacturers to include clinical data on safety and efficacy, generic drugs can be approved without repeating clinical trials. Regulators state that when equal pharmaceutical quality as well as equal drug exposure, by means of appropriate bioequivalence studies, has been demonstrated, the positive benefit-risk balance of the branded medicine also applies for the generic medicine [2]. Generic substitution would then be possible without further control.

There are many cases where prescribing generics is fully appropriate and vital to contain costs. Indeed, in several European countries generic prescriptions already account for more than half of all prescriptions, a level which has increased significantly over the last few years. For statins, proton pump inhibitors, antihypertensive drugs and many other drug classes, generic drugs have become the standard formulation.

However, for NTIDs in general and for certain immunosuppressive drugs in particular, there are concerns regarding the safety of generic substitution. These concerns are based on the assumption that in transplant patients even relatively small changes in immunosuppressive drug exposure can lead to serious clinical consequences, either referable to under-or overexposure to the drug.

Although the therapeutic efficacy of bioequivalent formulations of immunosuppressive drugs has been compared in several instances, it is reasonable to assume that these studies were statistically underpowered and could not detect potential differences in efficacy or safety [3].

The Association of the British Pharmaceutical Industry (ABPI) has issued a statement to avoid generic substitution for modified or sustained release formulations, for medicines with a narrow therapeutic window where there

[2]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003519.pdf

[3]http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

[4]Besides generic substitution we also recognize therapeutic substitution. In therapeutic substitution the prescribed drug is replaced with a chemically different drug within the same therapeutic category, e.g. bumetanide for furosemide; ranitidine for cimetidine. In generic substitution the prescribed drug is replaced with a chemically identical drug in the same dosage marketed by a different company. In this document only generic substitution will be discussed.

is evidence regarding the risk of adverse patient reactions or inadequate efficacy, for vaccines, for bio-similars, and for controlled release drugs.[5]

The concerns regarding generic substitution are based on several issues:

1 There are generic formulations of immunosuppressive drugs on the market that do not fulfil the currently applied bio-equivalence criteria for NTIDs. While in January 2010 the EMA issued its new guidelines on the investigation of bioequivalence, which came into effect in August 2010, a number of generic cyclosporine formulations were already registered. The registration of these generic cyclosporine formulations was based on the broader bioequivalence criteria (80–125%), and some of the generic formulations were not tested in both the fasted and fed state despite the recommendations of the Committee for Human Medicinal Products of the EMA. Some of these generic formulations do not fulfil the current bioequivalence criteria and their registration would not be assigned in case they would be re-evaluated today. For legal reasons, the registrations of these formulations cannot be revoked. However, their use should be discouraged unless they prove bioequivalence according to the new EMA guidelines.

2 Generic formulations are not necessarily bio-equivalent amongst themselves, although substitution of one generic for another is likely to occur. For registration of a first generic formulation bioequivalence with the brand name drug needs to be shown. Regulators argue that based on bioequivalence also therapeutic equivalence can be assumed and therefore generic substitution is made possible. With the new bioequivalence criteria there is a high probability that the deviation for mean AUC and Cmax of the generic drug is less than 10% compared with mean AUC and Cmax of the brand name drug. Strangely enough, subsequent generic formulations offered for registration only need to show bioequivalence with the brand name drug, and not with the other registered generic formulations. In daily practice, however, generic drugs will be substituted interchangeably, and it is sound to realize that the maximally allowed mean deviation for mean AUC and Cmax after switching from one generic formulation to another may be even higher than desired above. Consequently, in individual patients the differences in exposure between two different generic formulations may be even larger. Branded prescribing of all immunosuppressive preparations, including generics is an important measure to avoid uncontrolled switching between pharmacologically different preparations.

3 Relationship between exposure and surrogate parameter. It is important to emphasize, that the relationship between the measured surrogate pharmacokinetic parameter (e.g. C0, or C2) and exposure (expressed as AUC) may vary between formulations. For valid comparison between formulations, such data have to be provided, so that the regular drug monitoring can be performed under valid assumptions.

4 Prescribers are not aware of the dispensing of alternative formulations by the pharmacist to the patient. When pharmacists substitute brand name drugs for generic formulations they should contact the prescriber, but in daily practice this is frequently not done. If the prescriber is aware that a substitution to a generic formulation is made in many cases an extra monitoring visit is scheduled, to check drug exposure. If the pharmacist substitutes one generic formulation for another it is even more likely that the prescriber will not be informed. Clearly, in view of the statement issues under B, the potential deviation of drug exposure in such cases may even be larger. The summary of product characteristics of tacrolimus mentions that patients should be maintained on a single formulation of tacrolimus and that changes in drug formulation or other changes in regimen should only take place under close supervision of a transplant specialist. Only if the initiative for generic substitution is in the hands of the transplant specialist can conversion to an alternative formulation be followed by appropriate therapeutic drug monitoring to ensure that systemic exposure to the drug is maintained within the therapeutic window. Currently, no country has a reliable system in place to notify the prescriber of a potential change from brand to generic medication, or from one generic formulation to another. Attributable to the lack of such a control system, the clinician's ability to monitor and safeguard any changes depends on the patient's self-declaration to the healthcare team, which obviously is prone to fail [4].

5 Successively providing patients with different generic formulations will lead to confusion and errors. There is no requirement for generic formulations to have a similar appearance as the brand name drug. Generic drugs often differ from the brand name drug and from one another, as is the case for packaging. Unless patients are well informed that the appearance of their medication can change, this may alarm patients and raise fears that a prescribing or dispensing error has been made [5]. In the setting of strong price competition, changes in purchase policy of either the pharmacist or the health insurance company will unavoidably lead to dispensing of numerous generic formulations over time. No doubt this will lead to further confusion of the patient and consequently to dosing mistakes. For transplant patients this may lead not only to serious clinical problems but could also negatively affect drug adherence. An even bigger potential problem appears if the patient has been subscribed

[5]http://www.abpi.org.uk/press/press_releases_10/050110.asp

sequentially with two different formulations of the same drug without knowing that the two formulations are substitutes for each other. In this case the patients may be exposed to a double dose of the same drug with high potential toxicity.

6 Generic substitution can give rise to a conflict between the interests of patients and other stakeholders. Patients might suspect that cost containment-driven generic substitutions could compromise the quality of their care. The presumption that the generic drug is equivalent to the brand name drug may perhaps seem logical, when in fact it is utterly fictitious: it may be true, but is not necessarily true [6]. The absence of evidence of differences is not equal to evidence of no differences. Likewise, the absence of evidence for equivalent efficacy and safety does not mean that the generics are not equally effective and safe as the innovator product but this is based on assumption. Surveys have shown that patients are concerned if their prescription is changed, even with their doctor's consent [7].

7 Discount contracts between pharmaceutical manufacturers and health insurance companies force pharmacists to frequently change the dispensed formulation. In several countries health insurance companies have the policy to require from pharmaceutical manufacturers substantial price reductions once the patent has expired. Contracts are renewed every 6 or 12 months, with the aim of re-negotiating further price cuts. As a result of this competition pharmacists are forced to dispense the formulations produced by the cheapest manufacturer recruited by a particular insurance company. This economically driven system leads to numerous uncontrolled generic substitutions, confusion and unavoidably error. The savings in drug cost do not take into account the overall costs related to patient care, as for example the increased need for therapeutic drug monitoring, and the cost of toxicity or rejection episodes related to switching formulations.

Recommendations

There are several generic formulations of immunosuppressive drugs available that fulfil the stricter bioequivalence criteria. If transplant patients are switched by the transplant physician involved in the care of these patients from the brand name drug to these particular generic drugs under controlled circumstances, then it is unlikely that this will have a negative impact on clinical outcome. However, additional visits and drug monitoring are necessary to assure such an outcome.

We do however fear that patients will be subjected to numerous subsequent uncontrolled substitutions of different generics, especially after a first generic substitution has been issued. The potential changes in drug exposure associated with these substitutions may lead to prolonged periods of over-or underexposure, to increased within-patient variability in drug exposure, which potentially may affect long-term outcome of these patients. The switch may also lead to confusion and medication errors. A major concern is that the transplant physician (practitioner) will often not be aware of a switch to a generic formulation executed by the pharmacist.

The ESOT is not opposed to the use of generic drugs. Immunosuppressive drugs are expensive and life-long immunosuppressive therapy of transplant patients is associated with high financial costs. We do acknowledge that savings in the cost of immunosuppressive drugs will benefit health care and society at large as long as the overall cost is not increased ascribable to additional patient care and drug monitoring. However, we strongly advocate to strictly regulate the process of generic substitution of NTIDs in our vulnerable patient populations.

To achieve safe and controlled generic substitution we propose the following guidelines:

1 Generic formulations of immunosuppressive drugs that do not fulfil the stricter bioequivalence criteria should not be used. Such formulations would not obtain registration today, according to the new guidelines on the investigation of bioequivalence implemented by the EMA. The use of these already marketed generics should be discouraged unless they prove bioequivalence according to the new EMA guidelines.

2 Substitution of the brand name drug for a generic formulation should only be initiated by the transplant physician. Only when the initiative for generic substitution comes from the prescriber, can appropriate monitoring of the drug blood concentrations be ensured. Pharmacists and health insurance providers should refrain from forcing generic substitution. The prescriber should maintain an appropriate degree of vigilance towards unexpected observations associated with generic substitutions and keep a low threshold for reporting irregularities.

3 Repetitive (consecutive) substitutions between generic formulations of the same drug should be avoided. Prescribers are unaware of such substitutions, while changes in drug exposure can be more pronounced compared to substitution from brand name to first generic. Moreover, successively providing patients with different generic formulations will lead to confusion and errors. Generic preparations should be prescribed as a specific brand.

4 Patients should be informed on generic substitution, they should be taught how to identify the different formulations of the same drug, and they should alert the transplant physician if an uncontrolled substitution is made. Pharmacists should play an active role in not only informing the patient on the newly prescribed

formulation when generic substitution is initiated by the prescribing physician, but also in protecting the patient from subsequent substitutions.

5 The simultaneous use of different formulations in the same patients should be avoided. Several drugs have different dosing strengths, and are dosed according to blood level or side effects. As a consequence, many patients have to use different dosing strengths to get the correct dose. Thus, in theory it is possible, that one patient takes different formulations of the same drug simultaneously, to meet the dosing requirements (e.g. because of different prescription patterns and needs, the change of the pharmacy and changes in the supplier of a healthcare provider). It is obvious, that this may lead to confusion (at the patient level) and rather unpredictable pharmacokinetics. The unawareness of the prescribed physician about the actual dosing pattern may further lead to ill-advised dose changes, and wrong assumptions. In addition, the simultaneous use of a different formulation will increase the variability of drug exposure, which is associated with outcome. As a consequence it seems important to emphasize, that in change of a drug formulation, all strengths should be substituted. This underlines the necessity of the transplant physician to initiate and supervise the generic substitution.

6 Prescribers who wish to continue using an original product for their transplant patients must be able to explicitly prescribe it. In most countries it is possible to add a comment or tick a box on the prescription to indicate that a particular formulation is requested. With this exemption code the prescriber indicates that he or she objects to generic substitution (e.g. ''Aut idem'', in France ''non substitutable'' in the Netherlands ''medische noodzaak'', in Switzerland ''medical need'', in Italy ''non sostituibile''). This is the most effective way to ensure that patients receive the products the prescriber wants them to take and to avoid uncontrolled generic substitutions.

7 The possibility of using a generic drug from the day of transplantation. If a patient would start with a generic drug from the day of transplantation then the exposure to the drug can be individualized during admission. However, there is risk of future switching, either because the generic drug is not available at the community pharmacy or because there are cheaper alternatives or for any other reason. A switch at such an early time point after transplantation, when the risk of rejection is highest, should be avoided.

8 As a transplant community we should aim to assemble data in support of the efficacy and safety of the generic immunosuppressive drug preparations in transplant recipients. Additional data on pharmacokinetics, applicability of TDM (LSS, trough, C2), as well as safety and efficacy in de-novo and maintenance patients would be important for a comprehensive assessment of a generic drug.

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