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CONSENSUS STATEMENT ON GENERIC SUBSTITUTION FOR IMMUNOSUPPRESSANTS WITH A NARROW THERAPEUTIC INDEX

Through this consensus statement, the Spanish Transplantation Society (SET) and the Autonomous Transplantation Societies of Andalusia, Catalonia, Madrid and Valencia, wish to convey the concern of organ transplantation experts regarding generic substitution for immunosuppressants with a narrow therapeutic index (cyclosporine and tacrolimus).

This concern has also been expressed by prestigious societies of international renown, including the American Society of Transplantation in its written statement addressed to the Food and Drug Administration (FDA), and by organ transplantation experts in consensus statements published in international journals[1,2,3,4,5].

Calcineurin inhibitors (cyclosporine and tacrolimus) provide first-line immunosuppression in organ transplantation and, to date; all attempts to substitute them with other immunosuppressants have failed. These drugs are characterised by:

1. Narrow therapeutic index. i.e., a small window between optimum efficacy and toxicity
2. High intrasubject pharmacokinetic variability
3. Formulation-dependent bioavailability
4. Serious clinical consequences in the event of overdose and under-dosing
5. Dosing controlled by monitoring blood levels

These characteristics make these drugs hard to manage. Despite this, they have contributed significantly to the achievement of excellent results in organ transplantation.

As organ transplantation experts, we understand that the use of generics can reduce pharmaceutical expenditure, and indeed, in our daily work we prescribe a great number of generics (antihypertensives, statins, diuretics, antibiotics, etc.). We will continue to do so as long as clinical objectives and cost savings are both achieved. However, in the specific case of narrow-therapeutic-index immunosuppressants, there are serious doubts as to whether organ transplantation results, in general, are comparable with results obtained when original formulations are used, and even whether they actually lead to reduced spending. The reasons for our concern are based on the following data:

1. Regulations on generic approval are based on bioequivalence tests versus the original formulation.

After the efficacy and safety of an innovator drug have been approved under strict regulations, and when the patent licence for that drug has expired, the generic approval is regulated by a simplified process. Specifically, regulations state that the generic drug must have the same molecule and show bioequivalence to the originator drug.

The FDA and the European Medicines Agency (EMA) consider that for a generic drug to be bioequivalent to the innovator drug, the 90% confidence interval (α-level of significance = 10%) in the ratio of the Test to Reference preparations for the Area Under the Curve (AUC) value of logarithmically transformed data should lie within the range of 0.80-1.25[6, 7, 8]. Since both formulations have the same molecule, the key issue in bioequivalence testing is to demonstrate similar oral bioavailability. When two equivalent pharmaceutical preparations are administered by this route, absolute bioavailability cannot be directly determined between them and the AUC is used as a surrogate for the degree of absorption and systemic exposure, and peak concentration (C_{max}) and time to peak concentration (t_{max}) are used as a surrogate for the absorption rate[9].

Furthermore, in practice, the confidence interval approach is used with logarithmically transformed data[10]; and the range of 0.8 - 1.25 for bioequivalence acceptance implies a difference of -20 to +25% in the rate and extent of absorption of the two products (generic and innovator drug). These acceptance limits are arbitrary and based on the observation that a difference in the active substance blood concentration of -20 to +25% is not clinically significant[11]. According to this data, it would be assumed that a maximum difference of 45% in the concentration of a narrow-therapeutic-index drug - which would be possible in the established range - will not have clinical consequences, something that is hardly acceptable in organ transplantation.

Moreover, the 90% confidence interval is a measure that is influenced by inter- and intra-subject variability[12] and this has a significant impact on whether the bioequivalence test is accepted or rejected. Also, its ranges depend on the magnitude of intra-subject variability for the reference drug, and the sample size; and the bioequivalence test compares the quality between the reference and generic formulations. Therefore, tighter intra-subject variability in innovator drug bioavailability makes it hard for the generic to fulfil acceptable bioequivalence criteria[13].

2. Population analysed to establish bioequivalence

Bioequivalence tests are typically performed in healthy volunteers in a randomised crossover study following the administration of the new product and innovator formula, measuring their concentration-time course. The main limitation of this method lies in the population used to confirm the bioequivalence. In the generic product, the study population usually consists of 12 - 36 healthy young adults, and the data are extrapolated to organ transplantation recipients. Therefore, this bioequivalence test does not take into consideration any variability caused by interactions with other drugs and diseases, or characteristics of patients and excipients[3]. This may change pharmacokinetics, and in fact there is evidence that the pharmacokinetics of calcineurin inhibitors differs in healthy subjects and in organ transplantation recipients[14]. Moreover, the bioequivalence test is based on a single dose, which is not exactly the best method for testing a drug whose absorption varies with time and above all, considering that bioequivalence, in itself, does not demonstrate therapeutic equivalence.

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3. Variability in results.

The analysis of the results obtained in organ transplantation using generic calcineurin inhibitors shows great variability, ranging from similarity to results obtained with the original formulation[15,16,17] to other results that demonstrate an extremely high incidence of acute rejection and graft loss[18,19]. In the latter case, in living and cadaveric donor *de novo* kidney transplant recipients without demographic differences between those receiving the original and generic formulations, the multivariate analysis showed that the generic drug was an independent risk factor for biopsy proven acute rejection (95% CI 1.26 - 4.9; p = 0.008) and that patients receiving this medication had a coefficient of variation of blood levels versus the innovator formulation of > 40% (39.7% vs 25.3%; p = 0.03), > 50% (18.2% vs 8.1%; p = 0.03 and > 60% (10.2% vs 2%; p = 0.01). On the contrary, other data have shown similar results to those obtained with the innovator drug, but with a constant finding: most of them result from conversion in stable patients with good renal function.

This variability is a cause for concern for the professionals treating organ transplant recipients, because it shows that there are differences - that have yet to be well defined - between the generic and the original formulation and this could lead to a reversal in results that have already been overcome.

Special mention should be made of transplantation in paediatric patients and those at immunological risk. In both cases, there is unanimity that generic drugs increase the rate of acute rejection.

Paediatric transplantation has particularly important implications. Bioequivalence tests are performed in healthy adults and results are extrapolated to a paediatric population, which has a different calcineurin inhibitor metabolism from adults. Therefore, bioequivalence data in adults cannot be applied to the paediatric population. In fact, the little data that we have on the generic tacrolimus in children show a high acute rejection rate[20]. This has brought the State of Florida to pass a law to make the innovator formulation of tacrolimus to be prescribed as a "medically necessary" brand [20].

Most current experience in generic formulations of calcineurin inhibitors has been gained with cyclosporine. Experience with tacrolimus is still limited to short-term use and mostly in living donor recipients [21,22,23].

4. Economic impact of generic immunosuppressants.

The aim of using generics is to achieve the same results as the original formulation at a lower cost. Current data do not confirm that this is the case. A comparative study between the two formulations conducted at the University of Vanderbilt showed that rather than making savings, spending actually increased[24] (Table 1).

Table 1. Comparative analysis of the annual cost per patient (in dollars) in *de novo* renal transplant recipients.

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	Neoral (n=247)	Generic (n=64)	p
All drugs	12605	14233	0.04
Immunosuppressants	7892	8979	
Non-immunosuppressive drugs	4708	5254	

5. Other immunosuppressants

In our opinion, an assessment should be made of whether other immunosuppressants used in organ transplantation such as mycophenolate mofetil, mycophenolic acid, sirolimus and everolimus should be included in the list of non-substitutable drugs. Also, their substitution for generics should be indicated by the specialist for the same reasons previously given for cyclosporine and tacrolimus.

In summary, in this paper we have tried to describe the division between the agencies that are in charge of approving drugs and the experts who perform the organ transplantations and follow up these patients in public hospitals. We therefore ask for the enforcement of the Government response to a question asked in the Spanish Senate (Senate, Legislature IX, General Registry, entry 42623; date: 21-06-2010) on the use of generics, which reads as follows: "With the aim of protecting patients' health, there are medicinal products that are excluded from the general rules on possible substitution, and they cannot be substituted by the dispensing pharmacist without the express authorisation of the prescribing physician. Such medicinal products include drugs that contain some active substances that are considered as having a narrow therapeutic index (the most widely accepted technical criterion is a ratio of less than 2 between the upper limit - when toxicity occurs - and the lower limit - when the drug is ineffective), including some immunosuppressants used in transplant recipients such as tacrolimus and cyclosporine." This is not adhered to by hospital medical managers whose objectives include prescribing these drugs using the name of the active substance, which means that the pharmacist can dispense the generic drug. This procedure also breaches the ministerial decree that establishes the regulations on non-substitutable drugs of September 2007.

In Spain, organ transplantation has followed a long and difficult path to attain the results that we now have, and to position our country where it is now, with its reputation for organ transplantations. Although we have not been consulted by hospitals or official agencies, we would like to convey our opinion as experts in the subject and we must ask - surprising though it may seem - that the regulation on non-substitutable drugs should be enforced. We are aware of the cost of immunosuppressants, but it is not clear that generics offer a saving in costs. What is indeed clear is that there is high variability of results, ranging from similar results to those obtained with the innovator formulation, to other truly catastrophic results.

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