

Bioequivalence of narrow therapeutic index drugs and immunosuppressives

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Abstract

Stricter bioequivalence criteria are in place for generics where there are narrow therapeutic indexes such as generic immunosuppressives, enhancing their acceptance despite limited published studies. No serious issues have been reported to date with generic ciclosporine despite being on the market in Europe for more than 10 years

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Regulatory bioequivalence rules for usual generics are well-established and already recognized. However, for narrow therapeutic index drugs and immunosuppressives, there are specific and tighter criteria in place.

Drugs with a narrow therapeutic index are defined by a narrow distance between the dosage that induces a desired effect and that dosage which already has a toxic effect. Typically, this ratio in the field of pharmacology is indicated by the quotient of LD50/ED50 (LD50 = the dose at which 50% of the animals die, ED 50 = the dose at which 50% of the animals show the desired effect). Alternatively, the quotient of LD5/ED95 can be used, which can better illustrate a non-linear dose-response curve.

For a perfectly safe drug, the ratio should therefore be very high. If in contrast the ratio is low, i.e. if a drug shows a value of only 3 or 4, this is called a "Narrow Therapeutic Index-Drug" (NTI), which must always be dosed with particularly high accuracy. Even a minor variation in plasma levels may lead sometimes to treatment failure on the one hand or inevitably to toxic effects on the other. Examples of such agents typically include immunosuppressants, digitalis, theophylline, and some anti-epileptic drugs.

The acceptance range of bioequivalence trials which is usually applied for a marketing authorization of a generic drug is 80.00-125.00% of the 90% confidence interval of the ratio of the test and reference products' AUC (Area Under the Curve) and Cmax (maximum plasma concentration). For drugs with a narrow therapeutic index, and especially for immunosuppressives, the European Medicines Agency (EMA) demands even greater accuracy in justified cases and therefore has set more stringent criteria although in practice ratios for authorized conventional generics usually differ on average by only 3 to 4 percent from their originator [1-4].

EMA's overhauled bioequivalence (BE)-guideline [5], in force since 2010, requires that for potential narrow therapeutic index drugs the EMA's Pharmacokinetic-Working Party (PKWP) [6] will evaluate if a generic drug newly submitted for authorization is to be thought of as an NTI and whether for this NTI actually stricter bioequivalence criteria have to be applied. It is important for a pharmaceutical manufacturer or applicant to know that there is no pre-casted list that names all such agents, but that all agents submitted for generic authorization will be evaluated by the authority on a case by case basis with regard to their NTI-requirements.

Examples where this has already been practiced are the regulatory requirements for ciclosporin and tacrolimus generics as described in a PKWP Questions and Answers- (Q & A) document published on the EMA website [7]. In the case of these two immunosuppressives, restricted bioequivalence criteria were set.

For ciclosporin, narrower acceptance intervals of 90.00-111.11% are required for both the AUC and the Cmax. Whereas, for tacrolimus the narrow acceptance interval is only required for the AUC but is not required for the Cmax.

This is because tacrolimus plasma levels show accumulation with repeated dosing, resulting in a lower relevance being given to differences in initial peak plasma concentrations.

The narrower acceptance range limits for the confidence intervals for NTIs (Fig.1) provide a greater confidence in the true bioequivalence for these drug substances. However, this requirement significantly increases the number of subjects necessary for the bioequivalence (BE) studies. Tacrolimus, for example, is a drug which is not merely an NTI, but additionally shows relatively high intra-individual variation in plasma levels. It has a relatively high coefficient of variation (CV), close to 30%, which would classify it as a highly variable drug. Even in bioequivalence trials of tacrolimus, when a conventional acceptance range is applied, this would typically necessitate enrolling a substantially higher numbers of trial participants than in the usual, BE-Guideline requiring a minimum of 12 to 24 subjects. One would need at least 40 subjects for a tacrolimus product, and in fact to demonstrate compliance with the EMA's mandatorily required, narrower acceptance limits, might require up to 200 to 300 subjects.

To increase the safety of generic immunosuppressives even more, it is also recommended that the summary of product characteristics (SPC) states that patients who are prescribed either a generic immunosuppressant after an originator or are switched in any other way, have their plasma levels monitored during the time of the switch to avoid potential rejection [8]. This is however similar to what is undertaken in normal clinical practice when patients are first placed on an immunosuppressant after receiving a solid organ graft.

Because of the issues concerning generic immunosuppressive medicines, Molnar et al recently undertook a systematic review and meta-analysis of all available studies since 1980 comparing generic with originator (innovator) immunosuppressive medicines [9]. The authors documented that acute rejection was rare in transplant patients given generic immunosuppressive medicines and the incidence of rejection did not differ between the groups. However, as recently stated, the methodological standard of the published studies included was very variable and follow-up times were short [10].

In the evaluation of the pooled pharmacokinetic data Molnar et al showed that the generics met the FDA bioequivalence criteria, but did not all meet the stricter EMA criteria [9]. It appears that the small number of patients in some of the included studies, and as a result the wide confidence intervals, significantly contributed to this finding. For statistical reasons, in order for results to meet the stricter acceptance criteria for immunosuppressives, requiring narrow confidence intervals, a sufficiently higher number of patients must be included in the trials [11].

This effect on subject numbers needed is illustrated by the wide confidence intervals found in immunosuppressive studies with less than 20 subjects. As reviewed in the paper by Molnar et al, only trials with approximately 50 to 70 patients were able to fulfill the EMA acceptance criteria [9]. In detail, their sub analysis of two randomized kidney trials showed that with a mean of 30 subjects, both failed to fulfill the stricter EMA bioequivalence criteria whereas the pooled sub analysis of seven non-randomized interventional kidney studies with a 53% higher mean sample-size of 46 patients did fulfill these criteria.

Notably, the mean ratios of the test and reference products' AUC and C_{max} in most of the reported trials were well within the expected range [12]; and were in fact only a few percentage points higher or lower than 100% (9). These data strongly suggest that there are no clinically important problems with generic immunosuppressive agents, especially with those that meet the EMA criteria, but rather that there are problems with the scientific value, relevance and interpretation of smaller studies.

It should also be noted that the EMA's precautionous narrowing of bioequivalence limits was specifically implemented for situations where it is suspected that plasma level-monitoring will - against the SPC advice - not be complied with; such as following a switch from an originator to a generic (7). This narrowing can therefore be seen as a "safety net" for the use of immunosuppressive generics. This suggests that generic immunosuppressive drugs, used in the correct manner by practitioners aware of their precautions, especially the requirement for monitoring of plasma levels at the time of switching, may indeed be considered to be bioequivalent and expected to produce outcomes that are similar to those produced by originator products.

This expectation is supported by the fact that generic versions of immunosuppressive medicines (i.e. ciclosporin) have been on the market in Europe for more than 10 years and authorities' pharmacovigilance systems have not identified any serious issues specific for generic immunosuppressants. Lack of any evidence of problems even after an estimated hundreds of thousands of prescribed and dispensed doses, should alleviate major concerns among clinicians and patients when considering or undertaking a switch. However, it is expected that further well-designed studies with a suitable number of patients will help to fully address any remaining concerns with generic

immunosuppressives. Further education among physicians about the need to reliably monitor blood levels in patients when first prescribed generic immunosuppressives will also be needed. Such activities may also help to enhance adherence to immunosuppressive medicines, which is a crucial concern in transplant patients (13).

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Narrow Therapeutic Index Drugs (NTIs)

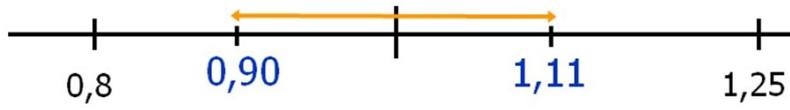


Figure 1: Tightened confidence intervals with a NTI, e.g. ciclosporin, required according to EMA rules for AUC and Cmax