Are generic immunosuppressants safe and effective?

Clinical experience is reassuring and regulation is strict, now we need definitive evidence

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Increasing use of generic drugs is essential to maintain comprehensive and equitable healthcare, given current pressure on budgets through, for instance, ageing populations. Initiatives among health authorities to promote generic prescribing include educational initiatives (which in the United Kingdom has resulted in high levels of prescribing of international non-proprietary name (INN) drugs in over 80% of all prescriptions), compulsory generic substitution in pharmacies, and patients paying extra "out of pocket" expenses for a proprietary drug.[1-3] Concerns remain, however, about generic prescribing or compulsory substitution in certain drugs and drug classes, including lithium, theophyllines, some anti-epileptic drugs, and the immunosuppressants evaluated in the linked study by Molnar and colleagues (doi:10.1136/bmj.h3163).[1] [4]

Strict regulations govern market authorisation for generic drugs [5]. Regulators such as the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) require manufacturers to show bioequivalence between a generic and a proprietary version of the same drug [6]. Subsequent meta-analyses have found no difference in outcomes between generics and originators across several classes of drugs, including cardiovascular medicines.[7]

Strict regulation helps to limit concerns about INN prescribing or generic substitution. Several studies have reported that proprietary drugs and their generic equivalents differ by only a few percentage points on accepted measures of bioavailability (area under the plasma concentration curve or AUC) and peak exposure (maximum plasma concentration or C_{max}).[8]

Regulation of generic immunosuppressants is stricter still. As a precautionary measure, the EMA has narrowed the acceptable difference in AUC between generic and proprietary versions. Marketing authorisation is granted only when the AUC ratio of test and reference product falls within a 90% confidence interval of 90% to 111%, narrower than the 80% to 125% interval accepted for other drugs. 8] The summary of product characteristics also recommends that patients prescribed generic immunosuppressive drugs have their plasma concentrations monitored during the switch to minimise the risk of rejection.[9] This recommendation echoes normal clinical practice, as patients are monitored in a similar way during initial treatment with an immunosuppressant after a solid organ graft.

In view of the continuing debate about the safety and effectiveness of generic immunosuppressive drugs, Molnar and colleagues undertook a systematic review and meta-analysis of all studies published since 1980 that compared generic with innovator (originator) immunosuppressive drugs for people with a solid organ transplant.[4]

They found that acute rejection was rare overall and that risk did not differ between groups of participants treated with a generic or an innovator drug.[4] The standard of methods of the published studies, however, was variable, with most studies having inadequate length of follow-up. Treatment failure can take time to emerge and can be missed by short term studies.[10]

Their analysis of pooled pharmacokinetic data showed that generic immunosuppressants are bioequivalent according to conventional regulatory criteria (90% confidence interval for the AUC ratio no wider than 80% to 125%), but they don't always meet the stricter EMA criteria (90% confidence interval no wider than 90% to 111%). The small number of patients in some studies probably contributed to this finding as lack of power leads to wide confidence intervals. Sample sizes would have to increase up to eightfold in some studies to achieve the tighter confidence intervals required by the EMA.[11]

For instance, the two trials of ciclosporin in recipients of kidney grafts had a mean number of 30 patients. In a pooled analysis, the AUC ratio failed to meet the EMA's criteria for bioequivalence. In a substantially larger pooled analysis of seven non-randomised studies (mean sample size 46), the EMA's criteria were met.

In most reported trials, the point estimates for AUC and C_{max} ratios were well within the expected range of being just a few percentage points higher or lower than 100%.[4] The problem might lie not with any clinically important difference between generics and originator immunosuppressants but with the poor quality of the available evidence and ensuing difficulties with interpretation. We should also remember that the EMA's narrowing

of the bioequivalence limits was designed to further protect patients who were unlikely to be monitored correctly after switching to a generic immunosuppressant.[12] Studies in patients who are correctly monitored, as instructed by the summary of product characteristics, could provide additional evidence that immunosuppressive generics, used in the correct manner and with precautionary monitoring in place, can indeed be bioequivalent to originator drugs and achieve similar long term outcomes.

Unfortunately, because of a relatively small number of eligible studies with hard to compare methods, and partly hampered by variable outcome reporting of crucial parameters, the study by Molnar and colleagues cannot establish with confidence whether or not generic immunosuppressive drugs are truly bioequivalent, effective, and safe.[4] We do know that generic immunosuppressive drugs, such as ciclosporin, have been on the market in Europe for more than 10 years and that pharmacovigilance systems have not identified any serious safety signals among the hundreds of thousands of doses prescribed and dispensed. While this observation is reassuring for clinicians and patients considering or undertaking a switch, bigger and better studies with longer follow-up are still required to fully examine any remaining concerns. In the meantime, clinicians could benefit from more education on the importance of monitoring plasma concentrations in patients who switch to a generic immunosuppressant. Monitoring is recommended by regulators, reassuring for patients, and might even improve adherence to treatment.[13]

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