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Generic Immunosuppressants in the Specialist Area of Transplantation – Consensus on Implications and Practical Recommendations

August 2011

Executive Summary

Solid-organ transplants are the best possible treatment for most people with organ failure, but the survival of the graft — and frequently the patient — depends on treatment with immunosuppressive medication to prevent rejection of the transplanted organ. Following patent expiries, the last two years has seen the introduction of an unprecedented number of generic immunosuppressants — notably for ciclosporin, tacrolimus and mycophenolate mofetil — for use in transplantation.

When used appropriately in the specialist transplant setting, generic immunosuppressants could help reduce NHS costs. However, the prime concern for all stakeholders — including transplant specialists, GPs, specialist hospital and community pharmacists, and commissioners — must be to ensure patient safety by avoiding inadvertent switching from immunosuppressant formulations on which patients have been stabilised by their transplant unit. Such medication errors not only risk potentially serious consequences for patients in terms of drug toxicity or graft rejection¹⁻³, but the financial cost of such complications could also outweigh any potential savings for the NHS resulting from the introduction of generic immunosuppressants.

The situation is particularly complicated in paediatric patients, who may be on various capsule, liquid and granule formulations of their different immunosuppressants. The potential for medication errors within such regimens is even more acute.

Despite previous warnings concerning the potential dangers for transplant patients⁴⁻⁷, inadvertent medication switches are still occurring, especially in the community setting. For this reason, we believe that it is essential to reinforce current advice by issuing clear, succinct and practical recommendations that can be universally applied:

1. The only practical way to ensure safety of transplant patients, both adults and children, is for any change in immunosuppressant treatment to be initiated in secondary care under specialist medical supervision, with appropriate monitoring.
2. All prescriptions, and related correspondence, should specify the brand on which the patient is stabilised, the dose and the frequency – be it the originator brand or a generic immunosuppressant.
3. Everyone in a position to influence safe prescribing of immunosuppressants, from transplant consultants through to the patients themselves, should be aware of these recommendations and seek to reinforce their implementation.

Background – licensing of generics

Generic products are not licensed on the basis of clinical assessment in the relevant patient group, but on simple bioequivalence assessment, generally in a small number of healthy volunteers. Thus licensed bioequivalence does not automatically mean clinical equivalence in practice⁸.

There may be no implications for patient safety when switching between branded and generic versions of many drugs in common use. But there are special considerations when using immunosuppressants in transplant patients. Not only is it critical to avoid any risk to the patient and the graft that may result from inadvertent medication switches, but it is also important to avoid potential drug-drug interactions in patients stabilised on medications for co-existing conditions.

Background – evidence in practice of risks to patient safety

Marked differences have been reported between different formulations in clinical practice, including:

- Need for dosage changes following a switch between formulations, to maintain appropriate blood levels – which necessitates additional patient monitoring¹
- Increase in biopsy-proven acute rejections which will require active patient management²
- Reduced long-term graft survival, which could mean a return to dialysis, the need for repeat transplantation or death³.

Background – ciclosporin, tacrolimus and MMF/ECMPS

Ciclosporin is a calcineurin inhibitor (CNI). It is well established that it is a pre-eminent example of a critical dose drug, and consequently should always be prescribed and dispensed by brand

Tacrolimus is, like ciclosporin, a CNI and a critical dose drug. As well as recently introduced immediate-release generic versions, the originating company has produced different immediate-release and prolonged release formulations. It is a particular cause for concern that some of these original and generic brand names sound very similar. For example, by the end of February 2010, the MHRA had

received 12 case reports involving prescribing/dispensing errors in association with the originating manufacturer's formulations of oral tacrolimus. Some of these had serious consequences such as acute rejection⁹.

Mycophenolate mofetil (MMF) is from a different class, that of the proliferation inhibitors. It is important to note that another form of mycophenolate is available as enteric-coated mycophenolate sodium (ECMPS). Since MMF is not interchangeable with ECMPS, it is essential to differentiate between the two drugs when prescribing and dispensing. (The patent on ECMPS has also not expired, and hence no generic versions are available.)

Background – costs of transplantation in context

Solid organ transplantation is highly cost-effective for the NHS¹⁰. For example, 3% of the NHS budget is currently spent on treatment for kidney failure. The average cost of kidney dialysis is £30,800 per patient per year. This compares with the indicative one-off cost of £17,000 for a kidney transplant, with costs for immunosuppression of £5,000 per patient per year. As a result, over 10 years (the median transplant survival time) kidney transplantation saves the NHS £241,000 or £24,100 per year for each year that the patient has a functioning graft. Acute rejection that may result from inadvertent medication switches clearly negates these cost savings if it leads to a return to dialysis. But successful treatment of acute rejection is also expensive, costing anything from circa £8,000 to £20,000 to manage, depending on whether or not a patient responds to steroids or requires more expensive antibody therapy.

Conclusion

Potential cost savings derived from substitution of generic immunosuppressants in transplantation must be weighed against risks to patient safety and the costs to the NHS arising from inadvertent switching.

Given past evidence of serious medication errors, the only practical way to ensure patient safety is for these immunosuppressants, including new generic versions, to be initiated only within the specialist hospital setting, with appropriate monitoring, and for all prescriptions and correspondence relating to that treatment to specify the brand on which the patient is stabilised – be it the originator brand or a generic.

For further information please see www.esprit.org.uk, send an e-mail to info@esprit.org.uk or call 01483 281321.

References

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Appendix

As at the date of this latest appendix (January 2012), the following originator brands and generics of ciclosporin, tacrolimus and the mycophenolates were available.

| Active ingredient | Original brand(s) | Generics |
|---|--|---|
| Ciclosporin | Neoral | Capimune, Deximune |
| Tacrolimus | Prograf (immediate release formulation, taken twice a day) Advagraf (sustained release, taken once a day) Modigraf (granules) | NB: all generics are immediate release Adoport, Vivadex, Tacni, Capexion |
| Mycophenolate mofetil (MMF) | Cellcept | Arzip, Myfenax <i>Unbranded MMF versions also from: Mylan, Dr Reddy, Sandoz</i> |
| Enteric coated mycophenolate sodium (ECMPS) | Myfortic | No generic available |

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