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Efficacy and Safety of PRescribing In T transplantation

ESPRIT Group Recommendations in Wake of Multiple Generic Immunosuppressants

As you will no doubt be aware, there are now multiple formulations of various post-transplant immunosuppressants available, notably ciclosporin, tacrolimus and mycophenolate, and these are all set to increase in the forthcoming months.

As a totally independent group of multidisciplinary healthcare professionals, dedicated to the safety and wellbeing of transplant patients, we thought it timely to let you know our latest recommendations on these agents, developed following in-depth review of the latest evidence available to us. For further information on the ESPRIT Group in general, including a full list of members, please visit our recently updated website at www.esprit.org.uk, where you will also find resources intended to help raise appropriate awareness amongst colleagues and patients alike.

Ciclosporin

Given that there are now three ciclosporin products available (including the original Neoral brand), the recommendations that we circulated in September 2009, when the first generic was launched, are now even more important. Ciclosporin is a pre-eminent example of a critical dose drug, and should always be prescribed and dispensed by brand, as also advocated by the BNF, MHRA, MIMS and other professional bodies, in order to avoid inadvertent switches between different formulations. Switching should only ever be contemplated in the specialist hospital setting, with appropriate monitoring.

Communications resources on ciclosporin are available for downloading/ ordering from the ESPRIT website – see www.esprit.org.uk/resources.cfm?category=Ciclosporin

Tacrolimus

In 2010 we have seen the introduction of the first generic tacrolimus, the immediate-release product Adoport. This has joined the original immediate-release Prograf, prolonged release Advagraf and Modigraf granule products. In 2011 we anticipate that there will be further generic introductions, which all have the potential to increase confusion and potentially undermine patient safety. Having reviewed the evidence to date as available to us, including the public assessment report on the regulatory submission for Adoport, and a number of

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clinical assessments reported this year, the considered view of the ESPRIT Group members is as follows:

- We can see no evidence to suggest that tacrolimus should be considered any differently from ciclosporin in terms of prescribing and dispensing practices. All tacrolimus prescriptions should be written by brand to avoid inadvertent switches, and to ensure that the patient is maintained on the formulation on which they were stabilised in the transplant unit, so helping ensure patient safety
- As with ciclosporin, switching should only be contemplated in the specialist transplant setting with appropriate monitoring

The detailed rationale for our firmly-held position is as follows:

- Tacrolimus is a similar drug (in the same class of calcineurin inhibitors) to ciclosporin and has essentially the same critical indications in transplantation
- There is currently no evidence that different immediate-release tacrolimus products can be safely interchanged. Issues encountered with ciclosporin only became apparent over the years, as experience grew. Consequently, we recommend a cautious approach given the strictly limited experience with generic tacrolimus to date
- The situation is further complicated by the fact that there were *originally* three different forms of tacrolimus (immediate-release Prograf, prolonged-release Advagraf and Modigraf granules). Now that a generic version of the immediate-release product is available, we believe that universal brand-prescribing is the only foolproof way to maintain patient safety. Anything else is likely to cause more – potentially dangerous – confusion at time when we should all be trying to minimise this. Indeed, we *have already* heard anecdotal reports of Advagraf and Adoport being confused
- Looking at the bioequivalence assessment for Adoport, upon which the licence for this first generic tacrolimus was granted in Europe, we note that for the 0.5mg dose strength, 219 healthy volunteers were needed to demonstrate bioequivalence within the 90-111% limits that the EMEA now recommends for critical dose drugs. (In contrast, only 43 subjects were necessary for the 5mg dose). This in itself indicates that there may well be variability in absorption and disposition, which could have clinical significance in transplant patients
- The only clinical evidence to date of which we are aware suggests a real need to monitor patients undergoing switching:
*Venkatamaranan et al*¹. studied the effects of switching 41 transplant patients from originator brand to generic tacrolimus. Given that 43% of

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patients had greater than 20% changes in blood concentrations, the authors consider it “prudent to measure tacrolimus levels when patients are switched to generic product”.

Similarly *McDevitt et al*². reported on 55 brand to generic conversions in the US and found that one out of every three to four patients required dose titration. They too commented on the prudence of post-conversion monitoring.

*Abdulnour et al*³ reported the results of four inadvertent switches from Prograf to generic tacrolimus in their paediatric renal transplant programme. Whilst there were no significant changes in blood levels or creatinine clearance in three, the fourth experienced a biopsy-proven acute rejection immediately after switching, with a significant change in creatinine.

References:

1. Venkatamaranan, R *et al*, Abstract no. 1741, Poster presented at ATC, San Diego, May 4th 2010
2. McDevitt, L.M *et al*, Abstract no.459, presented at Concurrent Session 63, ATC, San Diego, May 4th 2010
3. Abdulnour, HA *et al*, *Pediatr. Transplant.*, 2010, Aug 31 [Epub]

Mycophenolate

There are likely to be a number of different mycophenolate formulations introduced in the UK in the forthcoming months. Indeed, the first generics were introduced in the week that the patent expired on mycophenolate mofetil (CellCept original brand). The ESPRIT Group members met recently to assess the evidence currently available on the potential differences between mycophenolate mofetil (MMF) formulations and between MMF and enteric-coated mycophenolate sodium (ECMPS, Myfortic brand). It was noted that it is only the patent on MMF which expired in November 2010, not that on ECMPS.

The consensus conclusions of the Group were as follows:

MMF vs ECMPS

- There are definite differences apparent between MMF and ECMPS, most notably in terms of interactions with proton pump inhibitors (PPIs), which affect the pharmacokinetics of MMFs, but not ECMPS. Given the almost universal use of PPIs post-transplant, this is an important difference
- As a result it is **not** recommended that ECMPS and MMF products are interchanged. ECMPS should be prescribed by brand and patients should be made aware that they are different

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MMF vs MMF

- There is a high degree of variability apparent with all MMF formulations reviewed, be it the original CellCept formulation itself or new generics under test. This is in terms of both PK and reported side effects
- The evidence as to whether mycophenolate is a critical dose drug or not is equivocal
- Monitoring of blood levels is not routinely recommended, but there is some evidence that it may be desirable on certain occasions
- As there is no real evidence that different MMF formulations cannot be viewed as interchangeable, an immediate, blanket 'prescribe by brand' recommendation was not thought to be warranted at this stage, unlike with ciclosporin and tacrolimus
- Having said that, there is no real evidence that different MMF products **can** be safely interchanged either, SO the overall ESPRIT Group recommendation is that MMF formulations should only be changed in collaboration with the transplant unit. Patients should be fully informed of potential changes in MMF formulations and encouraged to report any changes experienced (especially adverse events) to their transplant unit. In this way collaboration between patients and their transplant units may enable real-life data to be collected and any potential issues highlighted as soon as possible
- Patients should also be made aware that they can self-report adverse events via yellow cards, although they should always discuss them with their transplant unit

We hope that you will find our recommendations helpful and would welcome any feedback at this important time for transplant patients. We are also looking to further develop our range of patient information and support materials, and would similarly appreciate any suggestions as to what transplant units would find most helpful. The best way to contact us is via our secretariat at info@esprit.org.uk.

Yours sincerely



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On Behalf of the ESPRIT Group Members

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