Cyclosporin as microemulsion—is it a new drug?

H.-H. Neumayer
5th Medical Clinic, University Hospital Charité, Humboldt-University-Berlin, Germany

Introduction

In this issue of *Nephrology Dialysis Transplantation* we report on a cohort of over 300 stable renal transplant patients who were switched from conventional cyclosporin to a microemulsion formulation of cyclosporin. We pose the question whether or not such a change in regimen would be beneficial for these patients.

Cyclosporin in transplantation

Cyclosporin is a difficult drug to use; however, we are delighted to have it. Without any doubt, cyclosporin has dramatically improved long-term graft survival in renal transplant patients and opened the possibility of successful transplantation of vital organs such as the heart and the liver. Nevertheless, despite major advances there are significant drawbacks, and a number of practical problems persist. For instance, 10 years after renal transplantation roughly one-half of the patients have lost their grafts, either as a result of acute rejection episodes or as a result of what is called 'chronic rejection' but might perhaps be better designated 'chronic graft failure'.

With this in mind, a debate continues on key issues such as: ‘What is the ideal dose?’, ‘What is the best way to monitor this drug?’, ‘Are measurements of trough levels adequate?’ and with regard to over-immunosuppression with the inherent risk of nephrotoxicity ‘What is the magnitude of the risk?’.

Problems with conventional cyclosporin

There is considerable variation in the pharmacokinetics of cyclosporin within and between individuals, and drug levels in any given person are hard to predict. Specifically the bioavailability of the drug shows marked intra- and interindividual variability. This is particularly true in patients with gastric or small-bowel disease, since the absorption of this highly lipophilic compound is influenced by bile flow, food intake, and gastrointestinal motility. However, the problem of variable absorption is not restricted to patients with gastrointestinal disease [1]. It goes without saying that both underdosing with the risk of insufficient immunosuppressive control, and overdosing with the risk of nephrotoxicity, are undesirable. Underdosing remains a major risk factor, since the incidence of early acute rejection episodes is the single most important predictor for long-term graft survival [2].

What is the ideal dose?

There is no consensus on this point. In predicting the 'adequate dose', the opinion of transplant surgeons is usually opposed to that of transplant nephrologists. In many centres of the United States the doses of cyclosporin are higher than in Europe, in the hope that the risk of acute rejection is reduced [3]. Europeans vividly recall the data of Meyers et al. [4], who showed clearly that cyclosporin nephrotoxicity is not invariably reversible in every patient. In addition, drug monitoring by measurement of monoclonal cyclosporin whole-blood trough levels is helpful but does not avoid toxicity in all patients [5].

What is the rationale for microemulsion cyclosporin?

As for other lipophilic drugs, e.g. theophyllin, it was hoped that cyclosporin in a microemulsified form would offer the following advantages: (i) faster and more consistent rate of absorption with less pharmacokinetic variability, (ii) improvement of dose linearity, and (iii) with regard to efficacy and toxicity a more advantageous profile.

In order to achieve this goal Sandoz Ltd. (Basle, Switzerland) provided a microemulsion formulation, and this new version of the 'old' drug is now on the market in many countries. The microemulsion has micelle-forming properties (<100 nm), is thermodynamically stable, self-emulsifying, and is little affected by the physiological state of the gastrointestinal tract. Thus intestinal uptake of the drug is less dependent on food intake and bile secretion, which leads to a more continuous absorption [1].

What are the risks and benefits?

The vagaries of cyclosporin pharmacokinetics are reduced to a certain degree by good clinical management [6], but the new microemulsion formulation offers entirely new perspectives.

Since the variability of pharmacokinetic parameters, such as AUC, C<sub>max</sub>, t<sub>max</sub>, and C<sub>min</sub>, of the microemulsion formulation is definitely reduced, systemic
drug exposure can be predicted with greater precision and rejection episodes should theoretically be reduced [7]. There appears to be consensus that terminal variance, i.e after 24 h, is less variable with the microemulsion formulation. However, because the bioavailability of the microemulsion formulation is increased by 30% on average compared to conventional cyclosporin, increased drug exposure is a potential risk particularly in malabsorbing patients. The increase in AUC could also increase the risk of nephrotoxicity and other adverse events such as hepatotoxicity or neurotoxicity [8]. Particularly with respect to the inherent risk of arterial hypertension in cyclosporin-based immunosuppression, the question arises as to whether the microemulsion formulation has advantages by causing higher peak concentrations but on average lower threshold concentrations. With regard to hypertension the patient has clearly a prolonged period of a 'drug-holiday' with the new formulation.

Potential benefits of the new microemulsion formulation may extend beyond kidney transplantation. In patients receiving primary liver allografts the new formulation clearly exhibited a superior pharmacokinetic profile compared with conventional cyclosporin. Moreover it has even been administered successfully to patients with cholestasis and rejection [9,10].

How should nephrologists use microemulsion cyclosporin?

Available evidence indicates that because of somewhat better gastrointestinal absorption, a 1:1 conversion from conventional cyclosporin to microemulsion cyclosporin will increase trough levels by approximately 10% on average. We believe that the improved bioavailability of the microemulsion formulation may lead to safety problems in some patients and therefore may present a hazard in patients whose drug levels are in the upper therapeutic range. Therefore I would recommend reduction of dose by approximately 10% in such patients. Dose reductions will be necessary in many patients, and in order to avoid the risk of overdosing I would recommend monitoring cyclosporin drug levels and serum creatinine concentrations 1, 2 and 4 weeks after the switchover.

It is of note that the dose ratio for conversion varies considerably and it has been claimed that occasionally even a somewhat higher dose of the microemulsion may be required. Monitoring uric acid concentrations and aspartate aminotransferase values is reasonable. Patients whose trough levels are not within the therapeutic range after 4 weeks should be followed at more frequent intervals.

One should not mix the old formulation with the new one. Long-term follow-up will be necessary and randomized double-blind trials may be warranted. Thus the answer to our initial question could be: 'New clothing for an old friend'.

## References


## Editor's note

Please see also the Original Article by Neumayer (pp. 165-172 in this issue).