Cyclosporine Metabolites: Are They Active?

Leslie M. Shaw

Knowledge about CsA metabolites is critical to our understanding and application of therapeutic drug monitoring to guide most-effective dosing of CsA in continuing efforts to minimize the risks of side effects while maximizing the opportunity for immunosuppression (1–3). This controversial issue has been the subject of many studies published in this and other journals and a topic of keen interest to many in the transplant field. In this issue of Clinical Chemistry, Copeland and colleagues report their investigation of the in vitro immunosuppressive activity of CsA metabolites they purified from urine of renal-transplant patients (4). A singularly important characteristic of this work is that they used well-characterized purified metabolites—essential in attempts to attribute immunosuppressive activity to a specific metabolite. Bowers et al. (5) emphasized the importance of using well-characterized pure metabolites in their recent investigations in which they also isolated a metabolite, which co-eluted with metabolite 17 in HPLC chromatograms, and identified it as hydroxydesmethyl-cyclosporine. The noteworthy point about the experimental design in the study of Copeland et al. is the use of three different types of in vitro tests of immunosuppression. Although in previous reports of studies of the in vitro immunosuppressive activity of CsA metabolites it was not possible for all investigators to use both well-characterized metabolites and the three types of immunosuppression tests used by Copeland and co-workers, it is interesting to note that the main conclusions drawn regarding the immunosuppressive activity of some metabolites relative to CsA, especially metabolite 17, are in accord with those of most of the other studies.

One of the conclusions of the Copeland group is that, except for metabolites 17 and 1 in one of the test systems (the secondary MLC), the immunosuppression relative to that of CsA for the studied metabolites was less than 10%—a conclusion that is in harmony with many but not all previous studies of this problem. Although one cannot extrapolate directly from in vitro tests to the in vivo circumstances of transplant patients, the authors make the reasonable suggestion that, in transplant patients with relatively stable metabolite/parent-drug concentrations, measuring M17 (16% of the activity of CsA in the secondary MLC and present in blood and tissues in relatively high concentration) in addition to measuring CsA in whole blood with a specific method is not justified for guiding the dosage of CsA. On the other hand, these authors suggest that, for patients with highly variable metabolite/parent-drug concentrations, further clinical studies are needed to answer the question of whether one should measure M17 concentration in whole blood in addition to CsA. Several studies of this sort are under way, and it is hoped that they will help to resolve this question.

The question of the toxicity of CsA metabolites is beginning to be addressed in several laboratories. Bowers et al. (6) have presented evidence for direct toxic effects of the carboxylated metabolite in the proximal region of cultured human renal tubules, comparable to that exerted by the parent drug in their system. Rosano and his group are exploring the possibility of preparing the relatively large quantities of purified metabolites needed to study the hemodynamic effects of CsA in in vivo animal models (T. Rosano, personal communication). They and others hope to investigate the in vivo immunosuppressive activity of CsA metabolites in appropriate animals as well, in the hopes that these models will closely mimic the clinical situation of transplant patients. T. Roby and I are investigating the acute hemodynamic effects of CsA in the perfused rat-kidney model and plan to investigate the effects of several pure metabolites in this model system. Thus, through the efforts of several groups of investigators, each looking at a particular aspect of CsA or metabolite activity, such as direct cellular effects or acute effects on the hemodynamic system, we can look forward hopefully to a further unfolding of answers to the problems associated with the fascinating, intriguing, but effective activity of CsA.

References

Hospital of the University of Pennsylvania, Department of Pathology and Laboratory Medicine, 3400 Spruce St., Philadelphia, PA 19104.