Clin Exp Immunol 2000; **121**:179–180

EDITORIAL REVIEW

Cyclosporin: nephro-protective as well as nephrotoxic?

P. W. MATHIESON *Academic Renal Unit, University of Bristol, Southmead Hospital, Bristol, UK*

(Accepted for publication 7 April 2000)

One of the earliest articles testifying to the immunosuppressive potency of the cyclic fungal peptide cyclosporin appeared in this journal in 1979 [1]. Cyclosporin was widely adopted into clinical practice in the l980s, becoming the mainstay of anti-rejection therapy in organ transplantation and also being used to treat numerous autoimmune diseases. In the succeeding two decades, much has been learned about the mode of action of the drug: its major immunosuppressive action in T cells is via inhibition of specific transcription factors such as NF-AT and NF-IL2A which mediate cytokine gene transcription, especially that of IL-2. Cyclosporin forms a complex with a cognate intracellular binding protein cyclophilin and inhibits its peptidyl-prolyl cis-trans isomerase activity. This leads to blockade of the Ca^{2+}/ca1modulin-regulated phosphatase calcineurin which is involved in activation of the transcription factors [2].

More recently, several newer immunosuppressive agents have become available, including tacrolimus, which has a similar mode of action to cyclosporin [3]. Unfortunately, it has become apparent that the adverse effects of cyclosporin and tacrolimus include nephrotoxicity [4]. Thus, clinicians involved in kidney transplantation face the peculiar situation of trying to protect the kidney from rejection using a drug which itself is capable of inducing significant kidney damage.

The introduction of cyclosporin was associated with a major improvement in early kidney transplant rejection rates and improved short-term graft survival [5], but disappointingly this has not been translated into improved long-term graft survival, and there is considerable concern that one reason for this may be that the drug's nephrotoxic effects negate its protective role. The adverse effects are dose-related and can be minimized to some extent by careful titration of dosage and blood levels, but nephrotoxicity remains a major limiting factor. The drug is also used in the treatment of many primary kidney diseases which are believed to be immune-mediated [6]; it seems particularly illogical to use a nephrotoxic drug in diseases where the main aim of therapy is to prevent nephron loss and preserve kidney function.

So should we discard cyclosporin? Unfortunately there are few alternative agents and, as mentioned above, one of them, tacrolimus, has similar nephrotoxic effects. Therefore rational design of new drugs, aiming to divorce the immunosuppressive potency of cyclosporin from its nephrotoxic effects, will depend upon an understanding of how it exerts its good and bad effects on the kidney. Cyclosporin reduces renal blood flow acutely by causing vasoconstriction and in the longer term by a variety of mechanisms including intimal thickening in blood vessels, hypertension and hyperlipidaemia, and also leads to interstitial fibrosis in the kidney. The haemodynamic effects can be antagonized to some extent by vasodilators such as nifedipine [7]; antioxidants have also been reported to protect against cyclosporin-induced renal injury [8,9], the assumption being that deleterious oxygen-derived free radicals are released as a consequence of renal ischaemia.

The typical histopathological feature of cyclosporin nephrotoxicity is interstitial fibrosis, and whilst this may simply be the end result of ischaemia, there is evidence that cyclosporin has other effects which promote the accumulation of collagen in the kidney [10]. Mediators of fibrosis include transforming growth factor-beta (TGF-β), and it is of considerable interest that production of this cytokine is 'spared' or even enhanced by both cyclosporin and tacrolimus [11,12]. Ironically, this could be both good and bad: good in the early stages since TGF-β may have immunosuppressive actions, but bad later on because of its potent pro-fibrotic effects. This point is well illustrated by a recent study which showed that cyclosporin's effects *in vivo* on lymphocyte proliferation and renal injury could be mimicked by TGF-β1 and abrogated by anti-TGF-β1 [13].

Another possible mode of action of cyclosporin is proposed by Rincon *et al*. in this issue of *Clinical and Experimental Immunology* [14] in a study of adhesion molecule expression in a rat model of chronic serum sickness. Cyclosporin treatment was associated with impressive reduction in renal injury as judged by proteinuria, even though circulating antibody titres and the extent of complement C3 deposition in the glomeruli were not altered. Cyclosporin-treated animals showed marked reduction in expression of the adhesion molecules CD54, CD18 and CD1lb/c in the kidney, and substantial reduction in the extent of leucocyte infiltration. This study neatly illustrates some of the complexities of dissecting the modes of action of cyclosporin: the authors suggest that cyclosporin has a direct effect on adhesion molecule expression and thereby inhibits cellular infiltration, but the results could equally well be explained by inhibition of cytokine production by infiltrating and/or intrinsic renal cells, preventing up-regulation of adhesion molecule expression and amplification of inflammatory injury. Detailed time course studies in cyclosporin-treated and control animals would be required to determine which was the primary effect. Cyclosporin's ability to limit production of so many proinflammatory mediators, thereby interrupting the

Correspondence: Professor Peter Mathieson, Academic Renal Unit, Southmead Hospital, Bristol BS10 5NB, UK.
E-mail: p.mathieson@bris.ac.uk

amplification of an inflammatory response, is one of the main reasons for the drug's potency; however, it also means that attempts to elucidate cyclosporin's mechanisms of action *in vivo* must be carefully designed to separate cause from consequence.

As illustrated by the example of TGF-β1 discussed above, it may prove impossible to separate entirely the desired effects of cyclosporin from its undesired toxicities, but continued attempts to do so are essential if we are to design rational new therapeutic strategies and get away from the uncomfortable feeling that our drug therapy could be damaging the very organ we are trying to protect.

REFERENCES

1 Calne RY. Pharmacological immunosuppression in clinical organ grafting. Observations on four agents: cyclosporin A, Asta 5122 (cytimun), lambda carrageenan and promethazine hydrochloride. Clin Exp Immunol 1979; **35**:1–9.

2 Clipstone NA, Crabtree GR. Identification of calcineurin as a key signalling enzyme in T-lymphocyte activation. Nature 1992; **357**:695–7.

3 Brazelton TR, Morris RE. Molecular mechanisms of action of new xenobiotic immunosuppressive drugs: tacrolimus (FK506), sirolimus (rapamycin), mycophenolate motetil and leflunomide. Curr Opin Immunol 1996; **8**:710–20.

4 De Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis 2000; **35**:333–46.

5 Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1998–96. New Engl J Med 2000; **342**:605–12.

6 Klein M, Radhakrishnan J, Appel G. Cyclosporine treatment of glomerular diseases. Annu Rev Med 1999; **50**:1–15.

7 Harper SJ, Moorhouse J, Abrams K *et al.* The beneficial effects of oral nifedipine on cyclosporin-treated renal transplant recipients—a randomised prospective study. Transplant Int 1996; **9**:115–25.

8 Tariq M, Morais C, Sobki S, Al Sulaiman M, Al Khader A. N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant 1999; **14**:923–9.

9 Kumar KV, Naidu MU, Shifow AA, Prayag A, Ratnakar KS. Melatonin: an antioxidant protects against cyclosporine-induced nephrotoxicity. Transplantation 1999; **67**:1065–8.

10 Vieira JM Jr, Noronha IL, Malheiros DM, Burdmann EA. Cyclosporine-induced interstitial fibrosis and arteriolar TGF-beta expression with preserved renal blood flow. Transplantation 1999; **68**:1746–53.

11 Li B, Sehajpal PK, Khanna A, Vlassara H, Cerami A, Stenzel KH, Suthanthiran M. Differential regulation of transforming growth factor beta and interleukin 2 genes in human T cells: demonstration by usage of novel competitor DNA constructs in the quantitative polymerase chain reaction. J Exp Med 1991; **174**:1259–62.

12 Khanna A, Cairns V, Hosenpud JD. Tacrolimus induces increased expression of transforming growth factor-beta 1 in mammalian lymphoid as well as nonlymphoid cells. Transplantation 1999; **67**:614–9.

13 Khanna A, Cairns VR, Becker CG, Hosenpud JD. Transforming growth factor (TGF)-beta mimics and anti-TGF-beta antibody abrogates the in vivo effects of cyclosporine: demonstration of a direct role of TGF-beta in immunosuppression and nephrotoxicity of cyclosporine. Transplantation 1999; **67**:882–9.

14 Rincon J, Parra G, Quiroz Y, Benatuil L, Rodriguez-Iturbe B. Cyclosporin A reduces expression of adhesion molecules in the kidney of rats with chronic serum sickness. Clin Exp Immunol 2000; **121**:391–8.