

PART XXI

WORKSHOP ON CYCLOSPORIN A IN CLINICAL PRACTICE

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J P Wauters [1] reported excellent results (83% one-year graft survival) using low dose Cyclosporin A with trough whole blood concentrations of between 100 and 400ng/ml. This corresponds to serum or plasma in the range of 20–80ng/ml. At these low drug concentrations the mean serum creatinine was 135 μ mol/L, exceeding 150 μ mol/L in only three of 27 kidney graft recipients. On the other hand, O'Donovan et al [2] found that transplant recipients with the highest blood Cyclosporin A in the first three days on 10mg/kg/day (or less) later had the least number of rejection episodes, the lowest serum creatinine and the best graft survival. However, since the O'Donovan team also adjusted the dosage to provide low whole blood concentrations (200–400ng/ml), it must not be concluded necessarily from these results that high doses are more effective than low doses. M Slapak et al [3] reported the results of a triple drug regimen (initially Cyclosporin A 12mg/kg/day, azathioprine 1mg/kg/day and prednisone 30mg; after one month Cyclosporin A 3mg/kg/day, azathioprine 0.75–1mg/kg/day and prednisone 15mg, the latter being discontinued after six months). The aim of the triple drug regimen was to keep the dosages so low that azathioprine would not be myelotoxic and Cyclosporin A would not be nephrotoxic. Despite poor HLA-A/B/DR matching the actuarial survival of cadaver kidney graft recipients was 78 per cent (2–42 months after transplantation). The only question is whether similar results could be obtained with low-dose Cyclosporin A alone without azathioprine. Zazgornik et al [4] administered Cyclosporin A in three divided daily doses in order to reduce nephrotoxicity. This regimen afforded lower peak values, but the authors were so far unable to confirm that this reduced nephrotoxicity. It was not clear whether in the final analysis it was the peak values or the areas under the curve which were correlated with nephrotoxicity. J Taylor et al [5] reported their experience with a treatment protocol in which patients were treated with Cyclosporin A for three months and were then switched to azathioprine and prednisone. Five of 42 patients had steroid-resistant rejection episodes and had to be switched back to Cyclosporin A. Because of late loss of grafts due to rejection in a further 11 patients the authors

consider that switching from Cyclosporin A to azathioprine and prednisone as a routine measure after three months is no longer justified.

The second part of the workshop was devoted to the use of Cyclosporin A in treating acute steroid-resistant rejection in patients receiving azathioprine. S Lamperi et al [6] treated steroid-resistant rejection episodes in 12 patients with 5mg/kg/day Cyclosporin A intravenously for five days. Cyclosporin A was then continued orally and azathioprine was tapered off. The rejection episodes responded satisfactorily to Cyclosporin A in all cases, as judged clinically and from fine-needle biopsy findings. M Sobh et al [7] obtained similarly good results in the same indication with a dose of 12.5mg/kg/day Cyclosporin A orally. Only three of 21 patients failed to respond to Cyclosporin A. F W Ballardie et al [8] treated steroid-resistant vascular rejection in patients on azathioprine by switching to Cyclosporin A at an initial oral dosage of 15–17mg/kg/day. Rejection episodes resolved in eight of 11 kidney graft recipients, and failed to resolve in three. Alexopoulos et al [9] tried a triple drug regimen of low-dose Cyclosporin A (1–8mg/kg/day), azathioprine (0.2–1.6mg/kg/day) and prednisone (0.2–1mg/kg/day) to treat steroid-resistant rejection in 20 patients on azathioprine, 18 of these patients responded. The only side effect was an exacerbation of hypertension in 12 patients, which responded to drug treatment. R McGonigle et al [10] successfully treated nine of 10 patients with steroid-resistant rejection on azathioprine by switching to Cyclosporin A. On this regimen the overall results obtained by McGonigle's team were as good (84%) as those obtained with a regimen in which Cyclosporin A was used from the outset. They concluded from this that Cyclosporin A should be used selectively as a second line of treatment only, in patients who develop steroid-resistant rejection episodes on azathioprine. Their argument was that, since the overall results are equally good, this would avoid exposing patients to the risk of nephrotoxicity unless there was no alternative.

The third part of the workshop was devoted to side effects. De Plaen et al [11] noted hypertension in four of 10 bone marrow transplant recipients; in these patients there was a trend to increased body weight and a significant rise in serum creatinine, while plasma renin activity and plasma aldosterone were significantly lower than in the six normotensive patients. The authors concluded from this that Cyclosporin A may initiate hypertension without activating the renin-aldosterone system. The assumption that Cyclosporin A directly inhibits glomerular filtration and thus indirectly causes sodium retention, which in its turn leads to a rise in blood pressure, at the same time inhibiting the renin-aldosterone system, is in good accord with these results.

F Egidi et al [12] compared the severity of tubulo-endothelial cell damage (evaluated by means of fine needle aspiration biopsy) with mean Cyclosporin A blood concentrations. They found no correlation and concluded from this that low Cyclosporin A values do not protect against nephrotoxicity but in fact increase the risk of rejection.

However, in the discussion of this paper it was pointed out that the correlation between high blood Cyclosporin A and nephrotoxicity, as evaluated clinically and on the basis of biopsy, has been shown very clearly in other centres

and that these results thus tend to cast some doubt on the reliability of fine needle biopsy as a technique for identifying nephrotoxicity.

At the conclusion of the workshop concern was expressed that the future trend will differ from practice in the early years during which Cyclosporin A was used, in that each centre will be experimenting with its own protocol and this may produce confusion. Without prospective controlled studies, in three to four years no one will really know which protocols are to be preferred. There is in particular a risk that patients will be exposed to double, triple or even quadruple treatment regimens, which could be replaced equally well by low-dose Cyclosporin A alone.

Papers presented

- 1 Wauters JP, Burnier M, Gilliard N, Stauffer JC. *Low-dose Cyclosporin A therapy allows avoidance of nephrotoxicity*
- 2 O'Donovan R, Compton F, Verbi V, Bewick M, Parsons V. *Higher Cyclosporin A levels in the first three days post-transplantation are associated with fewer rejection episodes, lower serum creatinines and significantly improved graft survival at 12 months*
- 3 Slapak M, Geoghegan T, Digard N, Ahmed K, Sharman VL, Qerchi G, Crockett R. *The use of low-dose Cyclosporin A in combination with azathioprine and steroids in renal transplantation*
- 4 Zazgornik J, Schindler J, Balcke P, Kopsa H, Gremmel F, Derfler K, Kretschmer G, Piza F. *Prevention of nephrotoxic Cyclosporin A peak concentrations by daily drug division in three equal portions*
- 5 Taylor J, Horsburgh T, Feehally J, Veitch PS, Walls J, Bell PRF. *Elective conversion from Cyclosporin A to azathioprine at three months*
- 6 Lamperi S, Carozzi S. *Cyclosporin A in the treatment of acute kidney allograft rejection steroid refractory*
- 7 Sobh M, El-Husseini F, Shebab El-Din A, Ghoneim M. *Cyclosporin A in the treatment of steroid resistant rejection episodes in living donor kidney transplants*
- 8 Ballardie FW, Clutterbuck EJ, Evans DJ, Rees AJ, Williams G. *Cyclosporin A for steroid-resistant acute vascular rejection of renal cadaver grafts*
- 9 Alexopoulos E, Daniilidis M, Sakellariou G, Hadjidimitriou C, Anasis P, Vyzantiadis A, Papadimitriou M. *Triple drug immunosuppression at low dose in high risk renal graft recipients*
- 10 Crowson MC, McGonigle RJS, Hopkinson G, Bonser R, Wilson I, Adu D, Michael J, Barnes AD. *Cyclosporin A in the treatment of steroid-resistant rejection in renal allograft recipients*
- 11 De Plaen JF, Ferrant A, Uten M, Uyttebrouck A, Michaux JL, van Ypersele de Strihou C. *Cyclosporin A induced hypertension in bone marrow transplantation*
- 12 Egidi F, De Vecchi A, Pagliari B, Moriggi M, Ponticelli C. *Lack of relationship between blood Cyclosporin A levels and nephrotoxicity at 'fine needle biopsy'*

