Cyclosporin withdrawal: to be or not to be!

J. Harold Helderman and Simin Goral

Vanderbilt Transplant Center, Vanderbilt University Medical Center, Nashville, TN, USA

Shortly after its isolation in 1976, cyclosporin A became the mainstay of immunosuppression for all forms of organ transplantation. Cyclosporin A dramatically improved patient and graft survival in renal transplantation and made widespread application of transplantation to other solid organs possible. Despite the clear advantages of cyclosporin over earlier 'historical' immunosuppression, observations made at the beginning of the cyclosporin era raised the possibility that long-term use of this particular agent can reduce renal allograft function and/or cause nephrotoxicity in native kidneys. The possibility of renal failure after long-term cyclosporin use was suggested by Myers and colleagues after their analysis of heart transplant recipients from Stanford University in 1984 [1]. The Myers observation in heart transplant recipients was the genesis of what can be called the cyclosporin dilemma, how to use this extraordinarily important immunosuppressive agent while avoiding the chronic nephrotoxic consequence. One strategy to accomplish this two-fold goal has been to employ cyclosporin in the peri-operative period and early graft experience, and then to withdraw the agent at a point at which graft accommodation has been assumed to occur. This strategy requires the provision of convincing evidence that chronic cyclosporin use is indeed 'the Achilles' heel' of kidney transplantation and is unavoidably nephrotoxic in a dose-unresponsive, irreversible manner, while also demonstrating the absence of important consequences from such a withdrawal [2].

Since the Myers observations, made in the early period of use, at the beginning of the 'learning curve', substantial new data have been accumulated to demonstrate that a safe and effective dose of cyclosporin can be chosen which avoids chronic nephrotoxicity. If we can convince the reader of this proposition, then we would submit that there is no rationale behind, and no need for, cyclosporin withdrawal, any negative consequence of which would be intolerable. Since the Myers observation, a multiplicity of prospective and retrospective analyses concerning the relationship between long-term cyclosporin use and progressive renal dysfunction have been made, almost all of which reach the conclusion that, after an initial reduction in renal function occurring within the first several months of transplantation, in general, renal function can be stable for up to 10 years of drug use [3-15]. Renal functional stability can be demonstrated even in cardiac

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Correspondence and offprint requests to: Dr J. Harold Helderman, Division of Nephrology, Vanderbilt University Medical Center, S-3305 Medical Center North, Nashville, TN 37232-2372, USA.
transplant recipients, a similar cohort of study individuals as that originally described by Myers and colleagues. Lewis et al., initially using the 1/creatinine paradigm, and later more precise measurements of glomerular filtration rate (GFR), show over 3 and later 5 years of follow-up, renal functional stability when cyclosporin was employed using 'optimal' dosing [11]. Monaco and colleagues revealed stable renal function after more than 4 years use in living-related recipients without progressive loss of GFR or organs [14]. Lewis also examined this issue in renal transplant recipients with the same conclusion [12]. These cited studies may be accused of having a short follow-up period, thus providing potential support for the possibility of withdrawing cyclosporin at a later time-point, avoiding the expected or putative cyclosporin chronic nephrotoxicity. Debunking this view are data defining stable renal function when cyclosporin is used correctly over 10 years in the kidney [13]. The most convincing study revealing the absence of chronic nephrotoxicity with long-term use was that of the multi-centre analysis of 1663 renal transplant recipients followed for 5 years, reported by Burke and colleagues [15].

It is therefore obvious that with optimal dosing of cyclosporin A, one can reap the benefits with respect to substantial improvements in graft survival, patient survival, reduced rejection rates, and reduced infections compared to earlier immunosuppression, while avoiding the major complication of chronic nephrotoxicity. If this argument is accepted, any important negative consequence which flows from the withdrawal of cyclosporin from the immunosuppressive package becomes intolerable. Is it possible to glean from the literature whether one exposes patients to important consequences upon cyclosporin withdrawal? We would argue that just such a paradigm exists. Firstly, Wrenchall and his colleagues found that sub-optimal dosing of cyclosporin is one of the most important predictors of acute, biopsy-proven rejection, a phenomenon known to be importantly associated with poor long-term graft outcomes from transplantation [16]. In the Opelz Renal Transplant Registry, with a major input from European centres, graft survival over time was best when cyclosporin dosing was the highest, and the worst in triple therapy regimens in which additional immunosuppressive drugs permitted clinicians to lower cyclosporin to the lowest maintenance dose. This again reveals that sub-optimal dosing is associated with worse graft outcome, obviating any benefit that might devolve for so-called improved renal function with lower cyclosporin dosing, and supporting the notion that an optimal dose both avoids rejection and chronic nephrotoxicity [17].

We would now like to turn to proving that cyclosporin withdrawal is associated with negative consequences which should not be tolerated in the face of proof that long-standing cyclosporin use is not intrinsically detrimental to kidney graft survival. The possibility that withdrawal from cyclosporin might be accomplished was initially ascribed to Rocher and colleagues, at what is now the Brigham and Women's Hospital, when they reported in 1984 withdrawal from cyclosporin to a prednisone-azathioprine regimen between 4 and 6 months after stable cadaveric renal transplant experience with a 20% improvement in serum creatinine [18]. The downside of such a protocol was a 1-30% acute rejection rate temporally linked to drug withdrawal with ~1/5 of the grafts lost. In 1988 one of us attempted to repeat the Rocher study with his transplant team, avoiding certain pitfalls felt to explain the previous results, which to many observers were unacceptable [19]. We argued that withdrawal should take place only in stable patients after 1 year when the absence of rejection episodes would be tantamount to evidence for effective graft accommodation, and that withdrawal should occur slowly over a 6-week period with the addition of azathioprine to a standard protocol of prednisone and cyclosporin to enhance background immunosuppression during cyclosporin taper. The study was conducted in a randomized, prospective fashion with one arm continuing to receive cyclosporin in a tapering dose toward 4 mg/kg/d, while the second arm underwent cyclosporin withdrawal under the umbrella of triple therapy. After 19 patients were randomized, six in the withdrawal arm experienced a temporally related acute rejection episode. Although not reported in the 1988 manuscript, there were no demographic differences in the two arms of study including the degree of match. In that study, while prednisone was not recycled at the time of withdrawal, withdrawal occurred over 6 weeks, and rather than recycle prednisone, the addition of full-dose azathioprine to what was a background of double therapy obviated the argument that inadequate immunosuppression in that arm alone accounted for the important results. Later, one of us performed an informal meta-analysis which evaluated 22 separate studies of cyclosporin withdrawal through 1994, studies accepted for analysis with no stringent criteria, under- standing that this protocol was a potential abrogation of the rules of this form of statistical analysis of literature [20]. In these studies, more than 1000 patients had been withdrawn at a time-point between 3 and 12 months after transplantation. Of the 1051, 349 experienced an acute, temporally related rejection. Although most of these individuals had their allograft 'rescued', graft losses were clearly described, hospitalizations occurred, and substantial increase in immunosuppression with its consequences was necessary. A more precise meta-analysis of 64 publications, with 17 found acceptable for the meticulous application of the meta-analysis statistic, was made by Kasiske and colleagues, clearly demonstrating a statistically significant risk of acute rejection regardless of the protocol used for withdrawal [21]. Although in the short run, the graft loss and patient mortality were similar in the withdrawn vs the maintained group, there was also no sustained improvement in graft function nor improvement in graft survival that should have been the consequence of cyclosporin withdrawal if that agent were driving chronic nephrotoxicity. In the face of
accumulating and convincing evidence that acute rejection episodes, especially those that occur late, are associated with, and are predictive of, decreased long-term graft outcome and chronic rejection, it would seem prudent to avoid this risk of acute rejection episodes attendant to cyclosporin withdrawal. Even in the update analysis by the Kasiske group which suggested that well-matched individuals undergoing a slow taper would have reduced rates of acute rejection, late acute rejection continued to occur consequent to taper, and no advantage over more than 5 years follow-up could be demonstrated in the withdrawing group, again debunking the concern for chronic nephrotoxicity, and permitting one to argue that even this reduced rate of acute rejection was unnecessary [22]. The two Kasiske studies taken together with the observations of Sanders in a high-risk group of African-American recipients [23] proves that there is a substantial risk of acute rejection after attempts of cyclosporin withdrawal in hitherto stable patients regardless of match or method. These acute rejection episodes require increased immunosuppression, hospitalization and increased cost, and are substantial arguments against conversion in stable patients without important side effects of the drug.

In summary, for the stable patient on ‘optimal’ dose of cyclosporin A without important side effects, cyclosporin withdrawal is an inappropriate clinical strategy because such an optimal dose can be safely used avoiding chronic nephrotoxicity, while such withdrawal, regardless of protocol, has the dire consequence of acute rejection which can and should be avoided.

References