Published in final edited form as:
Transplant Proc. 1991 August ; 23(4): 2178–2179.

Notes on FK 506

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Thank you for inviting me to this wonderful celebration. I once wrote my opinion, and meant it sincerely, that Roy Calne is one of the greatest surgical scientists in the world today, and for that matter in history. It could be a heavy burden to have this kind of talent. But Roy is someone who hardly seems to realize that he is larger than life. Roy, I salute you for all you have done, but even more for what you became personally while doing it. It must be a special pleasure for you to have here your senior colleague, Joe Murray, to whom you owe so much and who in his own turn owes so much to you, as he described last night.

My purpose today is to report briefly on trials with the new immunosuppressive drug, FK 506, which now has been in clinical use for 19 months. FK 506 has a chemical structure which is unrelated to cyclosporine (CyA). It is more potent than CyA and has many of the same properties, including suppression of T-helper lymphocyte activation. It suppresses interleukin-2 (IL-2) production and expression, and it inhibits the synthesis of other cytokines. FK 506 was discovered in 1984 and has been developed with astonishing rapidity. All of the publications about this drug have been since 1987. The rapid progress can be traced through the selected citations in the reference list.[1-10] This report is concerned with clinical trials.

ALLOGRAFT RESCUE

FK 506 has been used clinically to rescue more than 200 liver grafts from being lost to intractable acute or chronic rejection under CyA regimens.[5,6] Acute rejection can be controlled in three quarters of the cases, and chronic rejection in about half. If hepatitis is present, this condition may become worse after the switch.

Ten cardiac recipients have been switched 1 month to 1 year ago from CyA to FK 506, 2¾ to 50 months posttransplantation.[7] They had gone through multiple bouts of biopsy-proven rejection necessitating treatment with anti-lymphocyte globulin (ALG) preparations, azathioprine (AZA), and augmented steroids. In addition to stopping CyA and AZA, the steroids were lowered or stopped after switching to FK 506. One patient whose steroids were increased died of aspergillosis and a lymphoma 3 months after the drug change. The other nine are well. We believe that intractable heart rejection is a very attractive if not spectacular indication for switch to FK 506.

The most difficult rescue is of the kidney graft. We believe that this is due partly to the synergistic nephrotoxicity of CyA and FK 506 at the time of switch. In addition, the rejecting kidney quickly develops combinations of severely damaged glomeruli, tubular injury, immune-mediated arteritis, or interstitial fibrosis and has little capacity for functional recovery. However, of the 21 patients with failing renal grafts switched to FK 506, slightly more than half have had stabilization and improvement of kidney function.

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PRIMARY THERAPY

The largest experience using FK 506 as primary therapy has been with the liver. In 125 consecutive primary transplantations performed up to May 1990, the 6-month and subsequent survival of these patients has been >90% with graft survival of 88%.[8] These results have been better than in historical controls. The advantages of FK 506 are that it is highly effective in controlling rejection and that it can be used as monotherapy in most patients after the first several weeks, allowing minimal use of steroids. FK 506 can be nephrotoxic, but in these cases there was little evidence of permanent renal injury and striking freedom from arterial hypertension.

The results with thoracic organ transplantation reflect much the same story.[7] We have treated two double-lung and a heart and lung recipient 11 to 13 months ago with superb results. Further trials with the lung have been deferred to be sure that bronchiolitis obliterans will not be a threat in the complete absence of steroids, which were never used in these three patients. Of 30 pure heart recipients, including 8 children treated up to June 1990, 26 (87%) are living. All of the children and a number of the adults were taken off steroids within a few weeks, or never given prednisone.

The value of FK 506 probably is equivalent for kidney transplantation, although the high-risk nature of our renal case material makes this difficult to prove.[9] Through May 1990, 65 patients were given 66 homografts, all but 2 from cadaver donors. Thirty-five percent of the recipients were undergoing retransplantation. One of the 65 patients died of myocardial infarction for a mortality of 1.5%. Fifty-two (80%) are dialysis free 6 to 20 months postoperative. Graft survival is 83% in the nonsensitized patients and 73% in those sensitized. After 2 months, the prednisone requirement of patients with functioning grafts was 0 in 60%, 2.5 to 5 mg/d in another 15%, and 10 to 20 mg/d in the other 23%. Freedom from hypertension was noteworthy. Serum cholesterol levels have been low. We are now engaged in a randomized trial of CyA vs FK 506 regimens.

It may be that FK 506 will allow success with procedures that have been considered impractical, such as islet cell transplantation in humans. One of our islet recipients is insulin free more than 10 months after upper abdominal exenteration and liver plus islet grafting, and several more are close behind. In addition, three small bowel recipients (two with simultaneous livers) have been followed for 3 to 6 months.

TOXICITY

As with CyA, the principal liabilities of FK 506 are nephrotoxicity, neurotoxicity, and diabetogenicity. Hair and growth disturbances have not been seen, hypertension has not been a serious problem, and serum cholesterol and uric acid are not much elevated, if at all with FK 506. The most important factor promoting FK 506 toxicity is hepatic dysfunction, which profoundly influences FK 506 dosing.[10] Patients with seriously dysfunctional liver grafts may have astronomical rises in FK 506 in spite of reduction of the FK 506 doses. Under these circumstances, severe impairment of renal function will occur and neurotoxicity may escalate to coma or convulsions. The risk is particularly high during intravenous therapy. Even with good liver function, we believe that our intravenous doses as originally used were too high and that the total daily quantity of intravenous FK 506 probably should be one quarter to one third of the planned oral dose instead of the half dose which we used in our initial trials. In addition, we now believe that continuous (instead of bolus) FK 506 infusion should be used whenever the IV route is required.

AUTOIMMUNE DISEASES

The impact of FK 506 will almost certainly spread quickly beyond transplantation to autoimmune diseases.[10] We have already treated patients with the nephrotic syndrome secondary to a variety of glomerulonephritides, with remission of proteinuria in six of seven cases. The rapidity of response in autoimmune disorders has been particularly easy to follow in skin diseases. We have treated seven patients with psoriasis. The effects of FK 506 therapy were evident within 48 hours in all. The same rapidity of response has been seen in two patients with the wide-spread disfiguring open sores of pyoderma gangrenosum. Other high-priority autoimmune diseases include juvenile diabetes meilitus, autoimmune liver disorders (autoimmune hepatitis, primary biliary cirrhosis, and sclerosing cholangitis), and some of the enteritides.

CONCLUSION

FK 506 is a superior immunosuppressive agent that should improve patient survival after the commonly performed transplant procedures, make feasible transplantations that have been previously impractical, and allow immune intervention for serious autoimmune diseases.

Acknowledgments

Supported by Research Grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland.

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