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The Effect of FK 506 on Peripheral Blood T-Lymphocyte Subsets in Orthotopic Liver Transplant Patients

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ALTHOUGH the detailed immunosuppressive mechanism of cyclosporine (CyA) differs from that of FK 506, both CyA and FK 506 inhibit T-lymphocyte proliferation by blocking production of interleukin-2 (IL-2) either directly or indirectly.[1,2]

Peripheral T-lymphocyte subsets appeared to be influenced under the presence of CyA.[3–5] In rat, both CD4 and CD8 positive T lymphocytes were decreased in the peripheral blood in the presence of FK 506.[6]

In this study, we monitored the peripheral T-lymphocyte subsets in orthotopic liver transplant (OLT) patients to evaluate the association between plasma FK 506 trough level and T-lymphocyte subsets.

MATERIALS AND METHODS

Patients

This study consisted of 36 randomly selected plasma samples from patients who received OLT at the Presbyterian University Hospital, University of Pittsburgh, between May 1, 1991 and July 31, 1991. The initial immunosuppressant was FK 506 with a low-dose steroid. OKT3, antilymphocyte globulin (ALG), and azathioprine (Aza) were not used.

Peripheral T-Lymphocyte Subset Monitoring

Freshly isolated lymphocytes using Ficoll-Hypaque density method were stored in liquid nitrogen until the testing.

CD3, CD4, and CD8 monoclonal antibodies (Becton Dickinson, Mountain View, Calif) were used to stain the T-lymphocyte subsets as described earlier.[7] FACScan (Becton Dickinson) was used for the analysis.

Plasma FK 506 Trough Levels

The FK 506 trough levels were measured using the plasma isolated from the samples monitored for the T-lymphocyte subsets. The plasma FK 506 trough level was determined by enzyme-linked immunosorbent assay (ELISA) described by Tamura et al.[8]

RESULTS

FK 506 reduced the proportion of CD3 positive T lymphocytes in the peripheral blood, however, the magnitude of reduction was not influenced by the plasma FK 506 trough level (Fig 1).

The FK 506-treated patients had a decreased proportion of both CD4 and CD8 T lymphocytes compared with the

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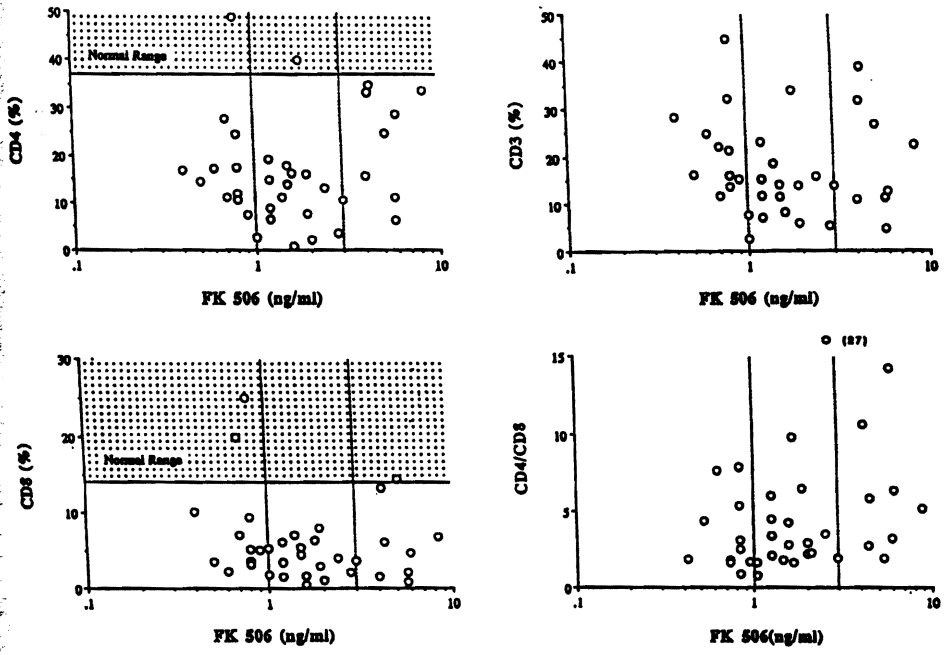

Fig 1. T-Lymphocyte subsets (CD3, CD4, and CD8) and CD4/CD8 ratio according to the plasma FK 506 trough level.

normal individuals with a few exceptions. Interestingly, the most significant suppression of CD4 or CD8 proportion was observed with a FK 506 plasma trough level of 1 to 3 ng/mL.

A trend of higher CD4/CD8 ratio was observed as the FK 506 trough level was increased, however, it was not significant.

DISCUSSION

FK 506 not only inhibits early phase of CD4 positive T-lymphocyte activation, it also suppresses CD8 positive cytotoxic T-lymphocyte generation.[1,9] Our study clearly demonstrated a decreased population of both CD4 and CD8 T lymphocytes. However, the most significant suppression was observed when FK 506 trough level was a range of 1 to 3 ng/mL in either subset.

The suppression was inconsistent when it was more than 3 ng/mL. This result differs from the in vitro experiment that indicated the dose-dependent efficiency of FK 506.[10] One possible explanation is that the in vitro study primarily focused on the functional study whereas our study reflects just cell population. Therefore, the FK 506 trough level does not necessarily need to reflect the suppressed number of CD4 or CD8 positive T lymphocytes. In fact, animal studies indicated that a higher incidence of CD8 positive T cells in the spleen or thymus was observed when FK 506 was administered.[11] The time lag between the monitoring results and FK 506 trough levels should not be overlooked.[11]

In summary, although further T-lymphocyte studies are in order in conjunction with the subset monitoring, a range of 1 to 3 ng/mL of plasma trough FK 506 levels seems to be favorable.

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