

Transplantation[®]

LETTERS TO THE EDITOR

EFFECT OF TROGLITAZONE ON CYCLOSPORINE WHOLE BLOOD LEVELS

Troglitazone (TGZ; Rezulin, Parke-Davis, Morris Plains, NJ) is a thiazolidinedione antihyperglycemic agent that has been shown to decrease hemoglobin A1c and decrease insulin requirements in patients with type 2 diabetes (1-4). It increases tissue sensitivity to insulin and decreases hepatic glucose production but does not increase insulin secretion (5). At doses used clinically, troglitazone decreases plasma levels of ethinyl estradiol and norethindrone in oral contraceptives by 30%, and terfenadine by 50-70%, possibly by inducing hepatic metabolism by CYP3A4 (6). However, clinically significant interactions with other drugs metabolized by CYP3A4, such as cyclosporine (CsA; Neoral, Novartis, East Hanover, New Jersey), have not been described in the literature. We report the effects of troglitazone on CsA whole blood levels in 11 stable renal transplant patients.

The medical records of all renal transplant recipients receiving TGZ at our hospital were reviewed. Of 12 patients, 11 had follow-up CsA blood levels available for analysis. All results are reported as mean \pm SD. The mean age was 54.5 \pm 11.6 years, and the mean time since transplantation was 20.5 \pm 18.2 months. All patients were receiving a stable CsA dose, and only one patient was receiving a drug known to affect the metabolism of CsA (diltiazem). The TGZ dose was 200-400 mg/day. The mean CsA whole blood level fell from 205 \pm 42 ng/ml at the time TGZ was initiated to 139 \pm 65 ng/ml after 1 week, a decrease of 32% ($P=0.0015$, paired t test). Six patients (50%) required a CsA dosage increase of 50-150 mg/day between 1 and 7 weeks after initiation of TGZ. The mean CsA dose at the time TGZ was initiated was 358 \pm 93 ng/ml, compared with 392 \pm 100 ng/ml after 4 weeks ($P=0.05$, paired t test) and 404 \pm 92 ng/ml after 12 weeks ($P=0.03$, paired t test). There were no concomitant changes in medications or obvious alterations in gastrointestinal function that could explain the decrease in CsA blood levels. Despite continuous administration of diltiazem in one patient, the CsA level fell by 53% after initiation of TGZ, and 7 weeks after initiation of TGZ, he suffered a Banff grade II rejection with vasculitis requiring treatment with OKT3 (Orthoclone OKT3, Ortho Biotech, Raritan, NJ). The serum creatinine concentration increased 30% from baseline in one other patient and was attributed to increased CsA dosage.

Troglitazone may be a useful antihyperglycemic agent in some transplant recipients with type 2 diabetes. However, it can lead to a reduction of CsA whole blood levels, possibly by inducing hepatic metabolism by CYP3A4. We have not used troglitazone in combination with tacrolimus to date, but we expect that the potential for decreased tacrolimus levels exists. Therefore, we recommend more frequent monitoring of either CsA or tacrolimus levels as appropriate after initiation of troglitazone, until a new steady state immunophilin level is achieved.

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CHIMERISM AND CLONAL EXHAUSTION

In their recent review, Bishop et al. (1) appropriately emphasized the essential role of donor leukocyte chimerism in the induction of "high-dose/activation-associated tolerance" (clonal exhaustion). While generously citing our discovery of

persistent post-organ transplant chimerism (2, 3), the authors attributed to us a hypothesis (i.e., "GVH-induced tolerance associated with chimerism" [1]) that could be construed as fundamentally different than theirs.

In actuality, the events after organ transplantation were explained in the cited articles "by responses of co-existing donor and recipient immune cells, each to the other, causing reciprocal clonal expansion, followed by peripheral clonal deletion" (2, 3). Thus, there is no inconsistency of the interpretations published from the Pittsburgh and Sydney laboratories except for the belief of Bishop et al. (1) that the clonal exhaustion is solely of the host leukocyte population. In our view, a mutually exhausting double immune reaction (host versus graft and graft versus host) must be invoked to explain the outcome in most transplant situations (2-5).

We also have proposed immune indifference as a second mechanism of organ acceptance. This is supported by the fact that the organ allograft is rendered progressively less immunogenic by replacement of its departed migratory leukocytes by recipient cells of the same lineages (2-4). In addition, many of the donor leukocytes are ultimately disseminated to nonlymphoid sites where immune activation does not readily occur (e.g., skin and parenchymal organs) (3). Both the response (clonal activation) or nonresponse (indifference) of the immune system following transplantation are governed primarily by the migration and localization of the antigen (5).

REPLY TO "CHIMERISM AND CLONAL EXHAUSTION"

We agree with Dr. Starzl that there is some concordance between our two models of transplant tolerance, although we maintain that there is a difference in the immune mechanism. In both models, donor leukocyte migration to recipient tissues is central to the process, although in our model it is not necessary for this to result in persistent microchimerism. Both models also predict that the outcome of the tolerance process will be deletion or inactivation of alloreactive clones of T cells.

The major difference between the two models is in the immune events which link donor cell migration with recipient T-cell deletion or inactivation. The Pittsburgh group uses their observation of persistent donor-derived microchimerism in tolerant recipients to infer a limited graft-versus-host reaction mediated by "donor veto/suppressor cells, cytokine profile changes or enhancing antibodies" as the tolerance mechanism (1). Consequently, they have attempted to promote transplant acceptance by infusing donor bone marrow to increase the graft-versus-host reaction and subsequent microchimerism (2).

Our model is based on the paradoxical observation of massive upregulation of interleukin-2 and interferon- γ mRNA in the recipient lymphoid tissues of tolerant animals (3, 4). Parallel observations in immunological models of high-dose or activation-associated tolerance have led us to propose these as mechanisms of transplant tolerance. This leads to predictions different from those of the Pittsburgh model. For instance, we predict that increasing the amount of transplanted tissue and donor leukocytes promotes tolerance rather than rejection and that interfering with early immune activation by treating transplant recipients with some kinds of immunosuppressive drugs reduces tolerance. We have tested both these predictions and found that they are supported by experimental evidence (3, 5, 6). We believe that definition of the immune mechanism of this powerful model of transplant tolerance will come from examination of the early

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immune changes in recipient lymphoid tissues rather than from determining the nature of persistent microchimerism.

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