Use of Subcutaneous Thymopentin in the Treatment of Steroid-Dependent Relapsing Minimal-Change Nephrotic Syndrome

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Dear Sir,

Thymopentin (TP5) is a synthetic penta-peptide which represents the biological active fragment of thymopoietin, a hormone isolated from the thymus [1]. It has been successfully used as an immunomodulatory agent in the treatment of a variety of immunological diseases, including atopic dermatitis, with few side effects [2]. In patients with minimal-change nephropathy (MCN), a history of atopy is commonly found, and relapses have been known to occur after food and other allergies [3]. Levamisole, another immunomodulatory agent, has been used to induce remission in these patients with some success [4]. Furthermore, we have recently observed the development of MCN in 2 patients who were previously thymectomised [5]. This suggests that lack of thymic hormones may be related to the pathogenesis of this form of nephropathy. Based on these observations and on the proposed immunopathogenesis of MCN, we have, therefore, decided to explore the use of TP5 in the treatment of relapsing MCN in a pilot study. In view of the result of a recent study which suggested that patients with relapsing MCN have a disturbance of T lymphocyte subset ratio [6], we also monitored the T cell subsets and function during the course of treatment in these patients.

Nine adult patients (7 males and 2 females ; mean age 27.8 years, range 19–35) with biopsy-proven MCN, more than 3 relapses upon steroid withdrawal in the past 2 years, on maintenance steroid of 0.15 mg/kg and in biochemically documented clinical remission for a mean of 1.9 (1st–3rd) months before the study

were given TP5 (Timmunox, Cilag AG, Switzerland) at a dosage of 50 mg subcutaneously 3 times a week for 12 weeks. Steroid dosage was maintained at 0.15 mg/day for 6 weeks after which the dosage was reduced by 50% at 8 weeks and stopped at 10 weeks. The patients were followed up for a mean of 10.3 (8–12) months. Subcutaneous TP5 was found to be ineffective in reducing relapses in these patients. Two relapses occurred while the patients were still receiving TP5. The relapse rate of 1.81 per post-treatment year calculated after a median follow-up period of 10.3 months (range 8–12) was similar to that 2 years before the treatment which was 1.67 per year.

Total WBC counts ($8,956 \pm 1,851/\text{mm}^3$) and the number of peripheral blood CD8⁺ or suppressor T cells ($672 \pm 218/\text{mm}^3$) were higher and CD4/CD8 or helper/suppressor T cell ratio (1.05 ± 0.69) and serum IgG level ($1010 \pm 286 \text{ mg/dl}$) were significantly lower in patients before TP5

treatment when compared to age- and sex-matched normal controls (corresponding values: $6,183 \pm 1,266/\text{mm}^3$, $532 \pm 278/\text{mm}^3$, 1.73 ± 0.67 , $1,204 \pm 199 \text{ mg/dl}$). However, except for the low serum IgG level, these abnormalities did not normalize with TP5 treatment and could be attributed to steroid treatment because they normalized after steroid was withdrawn despite continuous TP5 therapy. In the case of serum IgG, the possibility of spontaneous delayed normalisation following a previous relapse cannot be excluded. No significant difference in the levels of peripheral blood

total B (s-Ig⁺ or CD19⁺), total T (CD3⁺), helper T cells (CD4⁺), natural killer cells (CD16⁺) and interleukin-receptor-bearing T (CD25⁺) cells was observed among normal controls and patients at different phases of treatment.

Compared to normal controls, spontaneous and pokeweed mitogen-stimulated lymphocyte proliferation tended to be higher in patients while they were on steroid irrespective of whether they were on TP5 but no difference on phytohemagglutinin, concanavalin-A- and OKT3-stimulated cultures was observed among normal controls and patients at different phases of treatment.

We, therefore, concluded that TP5 given by a route and at a dosage and schedule which have been shown to have an immunomodulatory role in the response to conventional antigens [7, 8] and to be successful in treating atopic dermatitis (a condition not infrequently associated with relapsing MCN) is not effective in reducing relapses in patients with relapsing MCN. Our study on the peripheral blood lymphocyte subsets also suggests that in the latter group of patients, an increase in suppressor T cells and a decrease in helper/suppressor T cell ratio is due to a steroid effect and that TP5 does not appear to significantly alter the lymphocyte subsets or function in these patients.

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