

Treatment of Uveitis by Oral Administration of Retinal Antigen

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The concept of autoimmunity representing an "escape" from self-tolerance has prevailed for nearly half a century. The idea of "re-educating" the immune system in order to reinduce tolerance to self-antigens is also not new. Indeed, allergy injection immunotherapy has been based on that very concept for several decades. But the idea of the oral route of administration of autoantigens is relatively new, and at least three disease entities have been subjected to clinical trials testing the hypothesis that oral consumption of antigen would reinduce tolerance to the antigen and would therefore reduce the autoimmune process. Oral tolerization trials using myelin basic protein for patients with multiple sclerosis, type II collagen for patients with rheumatoid arthritis, and retinal S antigen for patients with uveitis have been conducted. We participated in the latter trial, collaborating with investigators from the National Eye Institute. The study was completed in 1996, and the results of that study were published in the *American Journal of Ophthalmology* in 1997 (Volume 123, pages 583-592). The essence of the study was to evaluate the effect and safety of the oral administration of retinal antigens as a treatment of ocular inflammation. In a Phase I/II randomized masked trial, patients with endogenous uveitis who were dependent on immunosuppressive agents were randomly assigned to receive retinal S antigen alone (10 patients), retinal S antigen and a mixture of soluble retinal antigens (10 patients) and a mixture of soluble retinal antigens alone (10 patients), or placebo (15 patients). An attempt was then made to taper patients completely off their standard immunosuppressive therapy over an eight week period. The primary study endpoint was time to ocular inflammatory attack. The secondary study endpoint was ability to taper patients completely off their immunosuppressive or cytotoxic medication within 8 weeks.

RESULTS: Time to development of the main study endpoint was not statistically significantly different for any of the four treatment groups. However, the group receiving the purified S antigen alone appeared to be tapered off their immunosuppressive medication more successfully compared with patients given placebo ($P = .08$), whereas all the other groups appeared to do worse than did those receiving placebo. No toxic effects attributable to any treatment were observed.

CONCLUSIONS: This phase I/II study is the first to test the use of orally administered S antigen in the treatment of uveitis. Although not statistically significant, patients given S antigen were more likely to be tapered off their chronically administered systemic immunosuppressive therapy than were the other groups tested.

The effort and expense involved in conducting this trial was vast. The results of the study were encouraging yet disappointing. Clearly, the preparation used was not "like penicillin for pneumococcal pneumonia." Still, the results were encouraging enough to suggest that additional efforts in this area of attempted oral tolerization/re-education are perfectly appropriate. The main challenge will be obtaining sufficient amounts of purified retinal S antigen or IRBP to enable conduct of a large, randomized study.