of up to 14 letters and 20/100 (20/50 to 20/200\textsuperscript{2}) for those with improvement of 15 or more letters. Because all patients enrolled in the TAP Investigation had lesions that had been judged by the enrolling ophthalmologist to be subfoveal, it is likely that the lesions in patients with improved visual acuity that were judged by the Photograph Reading Center graders not to be subfoveal were actually very close to being subfoveal. An ophthalmologist might consider verteporfin therapy or laser photocoagulation for juxtafoveal lesions, balancing, on the one hand, the potential to avoid the effects of photocoagulation-induced scotoma and the exploratory data in this letter against, on the other hand, the knowledge that laser photocoagulation is, at this time, the only treatment shown to be beneficial compared with no treatment for juxtafoveal lesions in randomized clinical trials. Additionally, however, the ophthalmologist should note that the exploratory data in this letter do not provide a precise answer as to how many relatively young patients with age-related macular degeneration and small juxtafoveal lesions would have an improvement of 15 or more letters in visual acuity following laser photocoagulation.

Improvement was not likely due to the clearance of significant areas of blood that were seen at the baseline examination because entrance criteria required that blood not extend under the center of the foveal avascular zone and blood as a lesion component was too occupy less than 50% of the entire lesion area. Furthermore, the presence or absence of blood was similar in patients with and without improvement. As a cautionary note, the number of patients with improvement was quite small; therefore, these exploratory analyses cannot be used to determine if there were any definitive associations between these baseline characteristics and improvement.

Patients who had improvement of at least 5 letters received a mean of 5.9 courses of verteporfin treatment over 24 months (of a maximum of 8 courses). Progression of classic CNV was least likely, and absence of leakage from classic CNV was most likely, among patients with improvement of 15 or more letters in both the entire study population and the subgroup with predominantly classic CNV at baseline.

It is unknown at this time why improvements of 15 or more letters in visual acuity occurred. Twenty patients (83%) with this amount of improvement at month 12 maintained that improvement at the month 24 examination. In addition, 16 patients (4%) who did not have improvement of 15 or more letters at month 12 had this improvement (relative to baseline) at the month 24 examination. Most patients with no improvement at the month 12 examination still had no improvement at month 24.

A small number of placebo-treated patients also had an improvement of 15 letters in visual acuity at the month 24 examination, although not more frequently than those assigned to verteporfin. As reported previously, at the month 24 examination, 8 (4%) of 207 placebo-treated patients had an improvement of 15 or more letters in visual acuity (including 2 patients who had a predominantly classic lesion composition at baseline) compared with 36 verteporfin-treated patients (9%). Also at this time, improvement of at least 5 letters but less than 15 letters occurred in 13 placebo-treated patients (6%) compared with 26 verteporfin-treated patients (7%).

The information in this letter should be considered when evaluating therapies that are shown to improve visual acuity outcomes in patients with CNV secondary to AMD. Furthermore, the exploratory finding that patients who had an improvement in visual acuity were more likely to have smaller lesions at baseline provides a potential reason for ophthalmologists to attempt to make an early identification of patients who may benefit from verteporfin therapy before significant lesion growth has occurred.

“Improvement After Verteporfin Therapy”

Writing Committee for the TAP Study Group

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AREDS Misses on Safety

I have read with interest the article pertaining to the Age-Related Eye Disease Study (AREDS) in the October 2001 issue of the ARCHIVES. However, I believe that while the results are of clinical interest, the findings of the AREDS pertaining to age-related macular degeneration (AMD) should be interpreted with caution. Although inorganic trace elements and vitamins are essential nutrients required for health maintenance, it is erroneous to address the use of such entities as therapeutics without a clear understanding and appreciation
of their relevant pharmacokinetic and pharmacodynamic properties. Furthermore, consideration of factors such as biological variability and dose-response, which express therapeutic action in terms of efficacy as well as toxicity, are in large part poorly defined within the AREDS study design. Characterization of the pharmacologic response to various high-dose vitamin and nutrient administration requires stringent assessment of population-, disease-, and formulation-specific variables that may influence the occurrence of adverse effects in ways not described in the AREDS.

For example, changes in drug disposition with age are characterized by alterations in lean body mass, which influences the volume of distribution and partition coefficients pertinent to fat-soluble vitamins, particularly α-tocopherol. Furthermore, individuals who use vitamin A1 as a source of beta-carotene should be advised that absorption of vitamin A1 (retinol) varies considerably depending on the formulation of the preparation as well as the amount of dietary fat an individual typically ingests.2 In addition, febrile infections and stress may markedly decrease serum retinol, whereas chronic renal disease may result in significantly elevated serum retinol, requiring the need for an alteration in intake.3 Moreover, the AREDS neglects to discuss assignment of causality, as well as the temporal relationship and outcome of reported adverse events, particularly those noted as “circulatory.” Furthermore, discussion of additive or synergistic effects, either observed or potential, of the AREDS therapy with various prescription and nonprescription products is lacking. The AREDS also does not address the need for continuing surveillance of the safety of vitamin and nutrient therapy for AMD in terms of elucidation of unexpected idiosyncratic reactions, an important yet complex task because of the ease of accessibility of such agents. Additionally, and perhaps of greater significance, it is unknown how the results of ongoing prospective trials of vitamin and nutrient therapy for disorders other than AMD will affect those currently following AREDS recommendations.4

Vitamins and nutrients are not only ubiquitous in nature and easily obtained from nourishing diets, they are also aggressively marketed by pharmaceutical companies eager to promote perceived as well as validated claims of health benefit. In addition, the clever marketing strategies of pharmaceutical companies, such as those promoting doses that “exceed AREDS recommendations,” demonstrate the need for clinicians to closely monitor vitamin and nutrient intake. I believe that the AREDS findings are inadequate in the elucidation of clear and concise safety guidelines for entities that are largely unregulated and widely promoted with an array of ingredients, formulations, and equivalency provided for public interpretation.

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