Vitamin A supplementation as therapy—are the benefits disease specific?1,2

A Catharine Ross

The report by Fawzi et al (1) in this issue of the Journal describes the results of a randomized, double-blind, placebo-controlled study conducted in a hospital in Dar es Salaam, Tanzania, to test whether vitamin A can reduce the severity of pneumonia. In this study, 687 children between 6 and 60 mo of age who were admitted to the hospital for nonmeasles pneumonia were randomly assigned to receive 100,000 IU (30 mg retinol equivalents; infants < 1 y of age) or 200,000 IU (60 mg retinol equivalents) vitamin A, or a placebo, on 2 consecutive days. The evaluation included mortality, duration of hospitalization, and the clinical severity of the pneumonia as assessed by a variety of symptoms. The report is important for being a carefully randomized, well-monitored, relatively large study conducted within an urban hospital setting to evaluate vitamin A as a treatment for an existing infectious disease. The authors report that vitamin A did not reduce mortality from nonmeasles pneumonia [relative risk (RR) = 1.63]. The 63% greater mortality in vitamin A–treated children was based on small numbers of children (13 in the vitamin A group compared with 8 in the placebo group) and was not statistically significant (P = 0.28). The lack of any beneficial effect and a trend toward increased mortality after vitamin A treatment is consistent with the results of community vitamin A supplementation trials in which there was no apparent beneficial effect (2), or with studies in Indonesia (3) and Nepal (4), in which high-dose vitamin A supplementation increased symptoms of respiratory illness (3) and mortality in infants (4).

It is now widely accepted that improving the vitamin A status of preschool-age children in populations at risk of vitamin A deficiency is an effective, low-cost means of improving child survival (5–7). Reductions in all-cause mortality after the administration of vitamin A have been shown in several community-based intervention studies. However, using data combined from several large trials, Beaton et al (6) calculated that vitamin A had no effect on mortality from respiratory diseases (RR of vitamin A compared with control = 0.99). This value is striking when compared with the highly significant reduction by vitamin A of all-cause mortality (RR = 0.73, P < 0.000) and of mortality associated with diarrhea (RR = 0.68, P < 0.000) and measles (RR = 0.74, P = 0.083) (6). A further meta-analysis of field trial data to assess the effect of vitamin A supplementation on pneumonia morbidity and mortality likewise led to the conclusion that, despite a significant reduction in all-cause mortality in both infants and children, there was no significant effect on pneumonia incidence (RR = 0.95) or pneumonia-related mortality (RR = 0.99) (2). The lack of benefit of vitamin A in pneumonia is all the more surprising because the epithelia of the trachea and respiratory tree are among the first tissues to show histologic changes characteristic of vitamin A deficiency.

One possible explanation for the lack of effect of vitamin A in Fawzi et al’s hospital study could be that the Tanzanian children in this study were not sufficiently vitamin A deficient to respond to treatment with vitamin A. The authors have begun an analysis of dietary intake that is reported in part in this issue (1). Most children had vitamin A intakes that were not far below the US recommended dietary allowance (8). Children in the lowest decile of vitamin A intake consumed about one-third of the recommended dietary allowance, but nevertheless, their outcomes did not differ from those of children whose vitamin A intakes were higher. Thus, the vitamin A status of most of these children may not have been particularly poor before their disease. Plasma vitamin A concentration during hospitalization was not determined. As the authors point out, plasma retinol is known to be depressed during acute infections (eg, malaria, tuberculosis, and measles). Nonetheless, it would have been informative, at least for comparative purposes, to know whether the plasma retinol concentrations of these children with active pneumonia were as low, for example, as those reported for South African children hospitalized for measles (110–120 μg/L), in whom Hussey and Klein (9) found vitamin A, administered in similar amounts, to significantly reduce measles-related mortality and the severity of disease as assessed by length of hospital stay.

Both high-dose vitamin A given at 4–6-mo intervals and low-dose vitamin A provided weekly have reduced all-cause mortality in at-risk populations (6), implying that vitamin A at either dietary or pharmacologic doses is effective when used prophylactically, as in community trials. It is conceivable, however, that the benefit of vitamin A as therapy during acute measles is not due solely to the repletion of tissue vitamin A, but perhaps also includes an adjuvant activity such as has been described for vitamin A and other retinoids (10, 11). In the case of vitamin A for measles therapy, there are no dose-response studies from which to ascertain whether lower doses of vitamin A, such as daily dietary intakes, might produce benefits similar to those observed in severe cases such as those studied by Fawzi et al.

1 From the Department of Veterinary Science and the Nutrition Department, The Pennsylvania State University, University Park.
2 Address reprint request to AC Ross, Department of Veterinary Science, The Pennsylvania State University, 115 Henning Building, University Park, PA 16802. E-mail: acr6@psu.edu.

after very large doses. Thus, even in the case of children hospitalized for measles, it is unclear whether the optimal strategy for delivering vitamin A has yet been elucidated.

Because each of these community- and hospital-based intervention studies seems credible, we may be forced to hypothesize that the effects of vitamin A during disease are, in fact, quite disease specific. If this is true, then elucidating the efficacy of vitamin A may require examination on a disease-by-disease basis. Fawzi et al (1) suggest that vitamin A might better be administered at discharge from the hospital rather than at admission, and for cases of respiratory illness, this now seems prudent. During hospitalization it is feasible to administer frequent dietary doses of vitamin A to prevent further vitamin A depletion or provide modest repletion for children who may truly be vitamin A deficient, while waiting until convalescence to administer larger prophylactic doses. In community settings, where the periodic delivery of high-dose vitamin A may be a necessity, practitioners should consider reducing the dose of vitamin A if children show signs of active respiratory illness.

At present, few generalizations can be made about the effects of vitamin A administered during infectious disease. The effects of vitamin A appear to be truly disease specific, with benefit being likely for measles and diarrheal diseases, but not for pneumonia. Perhaps this should not be surprising given the immune system’s exquisitely specific responses to different types of infection. In experimental studies, vitamin A status is clearly a factor in the response to some immune stimuli, although having little apparent effect on others (10, 11). Different infections, even those producing clinically similar illnesses, have unique etiologies and may elicit physiologic responses that may differ in important ways. The measles virus, the single causative agent of measles, elicits very different cellular and cytokine responses (12) from those elicited by the multiple species of viruses and bacteria that are causative of pneumonia. If future clinical studies are conducted on vitamin A supplementation during respiratory disease, attempts should be made to culture or otherwise identify the causative pathogen. Currently, we lack sufficient knowledge of the interactions between vitamin A and important immune response factors—lymphocytes, macrophages, and other cells; adhesion molecules; cytokines; chemokines; and receptors. However, as new and more sensitive immunologic methods become available, it should be possible to characterize changes in specific cell types and immune factors during the course of disease. Such information may provide important keys to understanding how nutrients such as vitamin A are capable—or sometimes not—of modulating disease outcomes.

REFERENCES