Intravenous Immunoglobulin Treatment for the Chronic Fatigue Syndrome

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Two articles in this issue of the Journal report opposite conclusions to the same question. In so doing, they reaffirm that even the most earnest efforts reveal truth slowly; but before we who do science relish too loudly this reminder of its challenging complexity, it is good to recall that many would have benefited by a clearer answer. It is preferable that Lloyd et al [1] and Peterson et al [2] would have agreed as to whether high-dose intravenous immunoglobulin benefits people with the chronic fatigue syndrome. Now, it remains difficult for some to resist the empiricism that a definitive answer would have thwarted. What considerations might help the reader in this?

The chronic fatigue syndrome is a poorly understood, heterogeneous disorder that is characterized by protracted and debilitating fatigue, feverishness, diffuse pains, depression, difficulty with sleeping, concentration, and other largely subjective problems [3-5]. Ideas regarding its nature are equally diverse. Some view it as reflecting a chronic infection with any of several known, or as yet unknown, pathogens. Others consider it to be nothing more than an expression of neurosis. Between this vast gulf of opinion lie a few facts, many assertions, and countless anecdotes. Some of each of these led to the current studies.

A review of the literature attests to the occurrence of this type of syndrome for centuries, and an equally long struggle to define its essence. In the last decade, interest in the process was renewed by reports that it is associated with profiles of antibodies to Epstein-Barr virus that suggest a persistently active infection [6,7]. More careful assessments eventually showed that the virus could not account for any substantial fraction of cases, but not before other unusual features of the syndrome were revealed [8-10]. Among these was the recognition that the outcomes of various immune measurements may differ between patients and control subjects. True immune deficiency is not a feature of this syndrome, but the cumulative findings seem to implicate a mild immune dysregulation. Some proportion of patients show evidence of immune activation, with mild increases in levels of antiviral antibodies or circulating immune complexes [6-8]. Others are found to exhibit mild reductions in immune function, such as natural killer cell activity [11,12]. Among the more consistent findings in the syndrome is the prevalence of immunoglobulin class and subclass deficiency, being upwards of 60% in some studies, including the present ones [1,2,13,14].

The impetus to assess immunoglobulin therapy in the chronic fatigue syndrome, was, at least in part, an effort to supplement some critical, albeit undefined, antigen-specific antibodies that could be deficient in these patients. In part, the trials attempted to exploit the known ability of high-dose intravenous immunoglobulin to ameliorate other disorders of immune regulation [15,16]. There is also a small study of intramuscular immunoglobulin therapy [17] and numerous anecdotes regarding the beneficial effects of intravenous immunoglobulin that begged confirmation through controlled investigations such as the current ones. Finally, the trials conducted by Lloyd et al [1] and Peterson et al [2] were compassionate efforts to fill a substantial void in the management of a syndrome that, while non-progressive and occasionally self-remitting, still lacks definitive therapy.

The two teams of investigators addressed the efficacy of intravenous immunoglobulin differently. Lloyd et al [1] treated 49 Australian adults monthly for 3 months with 2 g/kg of immunoglobulin or placebo. This dose is five times the standard regimen of immunoglobulin replacement therapy for hypogammaglobulinemia and equivalent to some of the highest doses used in treating idiopathic thrombocytopenic purpura and other disorders presumed to result from immune dysregulation [15,16]. In this study, 10 of 23 immunoglobulin recipients were considered improved, compared with only three of

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26 placebo recipients, a statistically significant difference. Peterson et al [2] treated 30 adults with 1 g/kg or placebo monthly for 6 months. About 20% to 30% of each group in this study reported symptomatic improvement, but there was no consistent benefit or treatment effect on functional status or well-being.

Why the disagreement in study outcome? To begin, there were obvious differences in these two studies with regard to sample size and immunoglobulin dosage. Only 28 subjects completed the American trial, a sample size that would have just missed yielding statistically significant results had the same percentages of treated and placebo recipients improved as in the Australian trial, namely 43% and 12%, respectively. The trial by Peterson et al [2] employed half the dose level of immunoglobulin as that used by Lloyd et al [1]. Assuming immunoglobulin replacement to be the determinant of efficacy, however, this dose should have sufficed. And, it may have sufficed even if its action were dependent upon correction of a putative immunoregulatory defect [16].

In addition, the Australian and American study cohorts may not have been comparable. The infectious or other experiential triggers of chronic fatigue may have differed for the participants of each study. Some people with this heterogenous syndrome may be more responsive to immunoglobulin than others. Importantly, American investigators required their subjects to meet Centers for Disease Control research criteria for the syndrome; the Australian investigators did not [3]. These criteria remain inadequately tested and have been criticized by some for being too exclusive and impractical, but adherence to these criteria in both studies would have aided their comparison.

Improvement among the Australian subjects was assessed only at 3 months after completion of therapy. The determination of clinical status was based upon interviews by a study physician. Curiously, no clinician assessments were made during treatment, and the study psychiatrist did not find significant improvement in treated subjects. The group from Minneapolis used a variety of quantitative self-assessment instruments to determine improvement. Similar measures used in the Australian subjects immediately prior to and 3 months after the final infusion showed no overall improvement from baseline. Thus, by some criteria, there was no clinical or psychologic improvement attributable to treatment in either study.

Given the differences between the two studies, there remains a residual possibility that immunoglobulin treatment is effective. Is it reasonable to recommend its use now pending future study? I think not. First, its expense is beyond the reach of most Americans, including unemployed or uninsured patients with chronic fatigue. Just the amount of drug administered in these studies would cost the average adult more than $10,000. Second, even the more optimistic Australian study provided no evidence that benefit accrues during treatment or would extend beyond 3 months after completion of treatment. Third, both groups demonstrated considerable adverse reactions during treatment, sufficient unto themselves to unblind the studies. In the study by Lloyd et al [1], phlebitis and constitutional symptoms lasting up to 10 days of each treatment month occurred in 55% and 82% of subjects, respectively. The study of Peterson et al [2] noted treatment to cause many of the same problems and a significant increase in headaches. For a population that is already debilitated by its symptoms, these additional reactions seem excessive.

Despite the conflicting conclusions regarding the efficacy of immunoglobulin, the two studies did yield important information and even agree in several areas. Each found their participants to be moderately impaired and even disabled by the physical and neuropsychologic consequences of their illness. Both studies found higher-than-expected rates of immunoglobulin subclass deficiency, which the Minneapolis team showed to be only partially replaced by immunoglobulin therapy.

Lloyd et al [1] undertook serial prospective cellular immune investigations of their study subjects. In accord with that group's earlier reports, reductions in delayed-typed hypersensitivity and blastogenesis responses were noted [18]. While it was not established that therapy led to an overall improvement in these immune parameters, it was shown that patients who improved clinically, for whatever reason, also improved immunologically. This is an important observation that will need to be pursued as an objective measure of clinical status in future studies of this syndrome.

REFERENCES