In the Literature

Apparent Lack of Benefit of Intravenous Immune Globulin (IVIG) for Clostridium difficile-Associated Diarrhea (CDAD)


Initial therapy with vancomycin or metronidazole fails for a number of patients with CDAD. In cases of severe disease, such initial therapeutic failure may lead to seriously adverse outcomes, including the need for total colectomy or, in the worst circumstances, death. A variety of therapeutic approaches have been recommended for patients with severe, refractory, or recurrent CDAD, and these approaches include intravenous administration of immunoglobulin. A recent retrospective review, for example, reported that this modality was associated with disease resolution in 9 of 14 patients [1]. There appear to be, however, no published reports that have included any sort of control group.

At a time when their institution was experiencing an outbreak of CDAD, including cases caused by toxigenotype 3 strains, the Pharmacy and Therapeutics Committee at the University of Pittsburgh Medical Center Presbyterian established a guideline for the use of IVIG for the treatment of severe CDAD. IVIG was approved for use only if patients met a set of (unvalidated) criteria for severity. After this policy had been in place for some time, a retrospective review of all cases of CDAD that occurred during 2001–2003 was performed. Of the 79 patients who met the criteria for severe disease, all had received oral vancomycin or intravenous metronidazole, 18 had received IVIG, and the remaining 61 had not received IVIG. The 18 IVIG recipients were then each paired with 18 subjects who had not received IVIG, and propensity score adjustment was used to control for confounding variables. The pairs were then analyzed as if each patient had received therapy by random assignment. Adverse outcomes (colectomy and/or death) occurred in 6 IVIG recipients (33%) and in 5 subjects (28%) who received only standard therapy.

This study was undertaken, at least in part, to yield data that would provide the basis for an estimation of the sample size needed in a prospective, randomized trial. The lack of any suggestion of a therapeutic benefit, however, provided the investigators no assistance in the development of such an estimate. Although the design and small sample size of this study preclude any definitive conclusions, the results do not support the use of IVIG as adjunctive therapy for severe CDAD.

Reference

Effect of Dexamethasone Therapy on MRI Findings in Tuberculosis (TB) Meningitis


Clinical trial data have demonstrated that administration of adjunctive dexamethasone therapy to adolescents and adults with TB meningitis is associated with improved survival but not with the prevention of severe disability [1]. The mechanism of this benefit is uncertain, but it is often assumed to be the result of amelioration of the inflammatory response and consequent prevention of neurologic injury. However, this investigative group previously reported that, although dexamethasone therapy was associated with a reduction in CSF protein concentration, it only marginally reduced IFN-γ concentration and did not affect a variety of other markers of inflammation in the CSF; also, this therapy did not suppress the response of PBMCs to mycobacterial antigens [2]. This same group of investigators, working in Ho Chi Minh City, Vietnam, have now examined the effect of dexamethasone on MRI findings in 50 consecutive patients from the clinical trial.

The patients in the clinical trial received standard first-line anti-TB treatment for 9 months, plus either placebo or dexamethasone, on a fixed schedule. Ventriculoperitoneal shunting was not available to the patients. Only 1 patient had a positive HIV antibody test result; antiretroviral therapy was not administered to this patient. MRI was performed at baseline and on days 60 and 270, and the findings were interpreted without knowledge of the patient’s treatment group. Because MRI required patients to be transported off site, it could not be performed for patients who were too ill; as a result, only 83 MRI results (for 43 patients) were available for analysis, and more MRI data were available in the dexamethasone arm than in the placebo arm because of the better clinical outcome of the patients in the former group.

Meningeal enhancement was present in four-fifths of the patients at baseline, and hydrocephalus (mostly communicating) was present in 77%. Cerebral infarction was detected in approximately one-tenth of the patients, and tuberculoma was detected in 64% (tuberculoma was parenchymal in 8 of 14 patients, ependymal in 3, and meningeal in 5). The proportion of patients with meningeal enhancement decreased during therapy. Nonetheless, enhancement persisted in ~40% of subjects at day 270, and there was no significant difference between treatment groups at days 60 or 270. The proportion of patients with tuberculoma increased from 64% to 74% after 60 days of treatment, but the predominant form shifted from
parenchymal (in 57%) to meningeal (95%) after 60 days, and there was no apparent effect of dexamethasone relative to placebo. Infarction, predominantly affecting the basal ganglia and internal capsule, was detected in 41% of subjects who underwent imaging studies at 60 days, compared with only 9% of subjects at baseline; infarction occurred at 60 days in 27% of dexamethasone recipients and 58% of placebo recipients \( (P = .13) \).

The high prevalence of tuberculoma, which actually increased after the initiation of therapy, is an unusual finding that may be the consequence of the routine use of MRI in an unselected patient population. The development of additional tuberculomas after the initiation of anti-TB therapy may represent, at least in part, an immune reconstitution phenomenon. However, this argument is countered by the fact that the incidence was not affected by the administration of dexamethasone. Although the presence of tuberculomas, a number of which involved only the meninges, was associated with more-prolonged fever, most cases were otherwise asymptomatic. In fact, tuberculomas were present in one-half of the patients who made a complete recovery.

In contrast to the apparent lack of effect of corticosteroid therapy on the presence of intracranial tuberculomas, dexamethasone therapy did appear to favorably affect the incidence of infarctions, many of which were first detected after the initiation of antimycobacterial therapy. Dexamethasone therapy was associated with a modest decrease in the incidence of hydrocephalus relative to placebo therapy, but this difference did not achieve statistical significance. Hydrocephalus should, in most cases, be treated by shunting, a procedure not available to these patients.

Thus, overall, this study demonstrates that the benefit of adjunctive therapy with dexamethasone may be related, at least in part, to a reduction in the incidence of cerebral infarction and, possibly, to a reduction in the incidence of hydrocephalus. However, neither of these differences achieved statistical significance relative to placebo therapy.

References


A Method to Reduce the Prion Content of Blood


Three cases of variant Creutzfeldt-Jakob disease are believed to have occurred as the result of transfusion of contaminated blood. Leukoreduction, now the rule in the United Kingdom and some other countries, is only partially effective in reducing infectivity; in the hands of Gregori and colleagues, leukoreduction diminished the infectivity of scrapie-infected hamster blood by 72%, a rate higher than was previously estimated. These investigators went on to demonstrate that infectivity was further reduced by use of a flow-through resin with high-affinity ligands, resulting in an overall reduction in infectivity of >1.22 log_{10} infectious doses. Because these resins also adsorb both normal and abnormal prion proteins from human cases of sporadic, familial, and variant Creutzfeldt-Jakob disease, it is possible that this system will have important applications.

Pandemic Influenza: Lessons from 1918


To develop a worst-case scenario for potential mortality due to pandemic influenza, the investigators examined available vital registration data from around the world for the years 1918–1920. During that period, mortality rates varied 30-fold across the countries evaluated, reaching a rate as high as 8% in an Indian province. A large proportion of this variability could be explained by discrepancies in income, with low-income regions having the highest mortality. Extrapolation of these data to the 2004 global population leads to an estimate of 62 million deaths from a similar pandemic, with 96% of the deaths occurring in lesser-developed countries.

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