EDITORIALS

Tuberculous Meningitis — New Approaches Needed

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The clinical effects of infectious diseases are determined by a complex interplay between pathogen and immune response, a dynamic exemplified by tuberculous meningitis. Despite being paucibacillary, tuberculous meningitis causes permanent neurologic injury and death in a high proportion of affected persons through local inflammatory complications and stroke. The maladaptive inflammatory response in tuberculous meningitis has not been fully characterized but may be amenable to modulation by glucocorticoids.

A trial conducted 20 years ago changed practice by showing that dexamethasone reduced mortality among patients with tuberculous meningitis in Vietnam.[1] This is the only intervention for tuberculous meningitis supported by strong evidence and is universally prescribed together with antituberculosis therapy. However, there have been lingering uncertainties about glucocorticoid use. The mechanism of protection is unclear: glucocorticoids do not reduce disability and do not consistently reduce concentrations of cerebrospinal fluid (CSF) immune mediators.[2] In addition, a clear benefit from dexamethasone was not shown among the subgroup of patients with human immunodeficiency virus (HIV) coinfection, which raises questions about efficacy in this key population that is disproportionately affected by tuberculous meningitis. Glucocorticoids are beneficial for the prevention and treatment of other inflammatory manifestations of tuberculosis in persons with HIV infection but have also been associated with harm, specifically HIV-associated cancers.[3]

In this issue of the *Journal*, Donovan and colleagues[4] report on a trial that aimed to resolve whether glucocorticoids reduce mortality from HIV-associated tuberculous meningitis. The investigators randomly assigned 520 HIV-positive adults with a clinical syndrome of tuberculous meningitis to receive adjunctive dexamethasone or placebo. The participants had high levels of immunosuppression (85% met criteria for advanced HIV disease), with most cases being probable or definite tuberculous meningitis. The trial was rigorously conducted, with almost complete 12-month follow-up — a monumental achievement in the context of a notoriously challenging disease to study.

Although there were numerically fewer deaths in the dexamethasone group than in the placebo group, the 95% confidence interval around the hazard ratio estimate included 1 (0.66 to 1.10), indicating no significant between-group difference for the primary end point. Findings were consistent in the per-protocol population and across most subgroups.

A major challenge for designing and powering clinical end-point trials for tuberculous meningitis is the lack of surrogate biomarkers for treatment response to enable early-phase efficacy studies. Donovan and colleagues enrolled an impressive number of participants, but it may be that a smaller true effect from dexamethasone exists and was not identified. The trial was powered to detect an approximately 30% relative difference in the risk of death, an ambitious expectation from a single intervention. Larger trials are needed for tuberculous meningitis, and infectious diseases in general, if we are not to

deprive vulnerable populations of interventions with more modest, but clinically meaningful, effects.

A real possibility is that dexamethasone has no benefit in HIV-associated tuberculous meningitis. It has been suggested that lack of efficacy from immunotherapy for other neurologic infections in advanced HIV infection is explained by relative immune hyporesponsiveness and dominant pathogen-mediated damage.[5] Although hyperinflammatory CSF profiles have been described in HIV-associated tuberculous meningitis, it is increasingly recognized that this compartment may not reflect underlying injury-inducing pathological processes.[6]

There is a wide spectrum of host responses to tuberculous meningitis,[7] and the use of a relatively blunt immunomodulatory tool such as dexamethasone in a population with variable degrees of immune dysfunction could be the wrong strategy going forward. A more targeted approach to immune modulation with therapeutics, such as tumor necrosis factor α blockers, and for specific clinical phenotypes may be required. This should be pursued in parallel with deeper mechanistic investigation using disease models of tuberculous meningitis to identify therapeutic targets and pharmacodynamic markers.

In the meantime, how should this trial influence clinical practice? The data show that dexamethasone does not improve outcomes in most patients with tuberculous meningitis and advanced HIV. However, dexamethasone is not associated with harm in this population, and in the context of a severe disease that kills or disables half its victims, even a small potential reduction in mortality — which was not excluded by this trial — may justify continued use.

Despite the negative result, this trial sends an unequivocal message: a plateau has been reached with existing therapies in tuberculous meningitis. Different approaches are required. Attention to low-cost nontherapeutic interventions, such as improvements in basic supportive management and earlier provision of therapy through better diagnostics and pathways to care,[8] may have large effects. Current trials are evaluating enhanced antituberculosis-drug regimens and aspirin (which has antiinflammatory effects at higher doses).[9] The tuberculosis community should be open to developing and testing even bolder interventions, including rifamycin-free drug combinations designed specifically for tuberculous meningitis,[10] delivered with the most promising novel candidates for host-directed therapy. Donovan and colleagues have shown progress can be made to reduce suffering from tuberculous meningitis, but there is still a long way to go.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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