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EDITORIAL

Corticosteroids for tuberculous pericarditis: can we learn from variability?

DESPITE EFFECTIVE antimicrobial therapy, tuberculous pericarditis is still associated with high morbidity and mortality. Adjunctive corticosteroids have been examined as an intervention to reduce inflammation and perhaps constrictive sequelae, and early studies suggested that this intervention improved outcomes.[1] However, a more recent large randomized placebo-controlled trial of adjunctive corticosteroids did not show any significant benefit on a composite endpoint of constrictive pericarditis, cardiac tamponade, or mortality.[2] The meta-analysis in this issue of the *Journal* by George et al. attempts to synthesize these discrepant pieces of data.[3] Similar to a recent Cochrane meta-analysis on this topic, they found that the large study by Mayosi et al.[2] outweighed the smaller studies, and no significant benefit for corticosteroids was demonstrated. The major additional contribution of George et al.'s article is a 'sensitivity analysis' that showed that one or two additional, large (1400 participants) studies would be required to move the preponderance of evidence toward a significant net benefit for corticosteroids in tuberculous pericarditis.

Such large studies are unlikely to be conducted, but is 'no corticosteroids' the final answer? A more nuanced view may provide insight. George et al.'s analysis demonstrated moderate to substantial heterogeneity among the studies analysed. Some of this heterogeneity may relate to the prevalence of human immunodeficiency virus (HIV) infection (67% of the patients in the large Mayosi study were HIV-coinfected, while two earlier studies likely had fewer HIV-coinfected participants), but subgroup analyses of HIV-coinfected versus uninfected patients did not demonstrate clear benefit of adjunctive corticosteroids in HIV-uninfected patients. However, recent work on tuberculous meningitis has demonstrated that patient genetics influence the inflammatory response to tuberculosis and modify the effect of corticosteroids, with 'high inflammation' genotype patients receiving significant benefit from corticosteroids, and 'low inflammation' genotype patients receiving no benefit.[4] This work likely has relevance for tuberculous pericarditis, and one could envision a trial in which baseline genotyping is obtained and only participants with 'high inflammation' genotypes are eligible for randomization into a corticosteroid arm. A genotype-based approach would target a group of patients most likely to benefit, which should permit a relatively small sample size.

Current guidelines provide conflicting recommendations, with the 2016 American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America recommending that adjunctive corticosteroids not be used routinely for the treatment of tuberculous pericarditis,[5] while the World Health Organization 2017 guidelines state that adjunctive corticosteroids may be used, with the justification that the potential benefit of preventing constrictive pericarditis outweighed potential harms.[6] Both guidelines provide conditional recommendations with very low certainty in the evidence, and clinicians are likely to prescribe adjunctive corticosteroids on a case-by-case basis. The next study of this topic should take advantage of newer tools to employ variability to patients' advantage and provide a more personalized approach to adjunctive treatment of tuberculous pericarditis.

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