IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Optimizing Antimicrobial and Host-Directed Therapies to Improve Clinical Outcomes of Childhood Tuberculous Meningitis

To the Editor—We read with interest the article by Thee et al [1], which reported high morbidity and mortality in children routinely treated for tuberculous meningitis (TBM) in 9 European countries, despite the low proportion of patients who presented with the most severe (grade 3) disease and ready availability of advanced supportive care [1]. The case-fatality rate in this study (n = 10/104, 9.6%) was lower than global estimates in a recent meta-analysis (19.3%; 95% confidence interval [CI]: 14.0–26.1%), but the risk of neurological sequelae among survivors was high (n = 45/94, 47.9%) and comparable with global estimates (53.9%; 95% CI: 42.6–64.9%) [2].

Optimal treatment for childhood TBM remains unclear, and research should focus on optimizing mycobacterial killing and minimizing deleterious immunological responses to prevent and manage disease complications [3]. We agree with Thee et al [1] that the use of intensified antimicrobial therapy containing high-dose rifampicin and other anti-tuberculosis drugs with good cerebrospinal fluid penetration should be advocated. Based on real-world data from South Africa, a high-dose intensified regimen for 6 months composed of isoniazid, rifampicin, and ethionamide at 20 mg/kg/day and pyrazinamide at 40 mg/kg/day is currently recommended by the World Health Organization as an alternative treatment option for childhood TBM [4]. However, longer-term treatment recommendations will be strongly influenced by 2 ongoing clinical trials to shorten TBM treatment and hopefully improve TBM outcomes in children (TBM-KIDS: NCT02958709; SURE: ISRCTN40829906).

A dysregulated host immune response with excessive inflammation and immune-mediated tissue damage contributes to TBM-related morbidity and mortality [3]. As the mainstay of host-directed therapy, corticosteroids have been shown to improve the TBM survival rate [5], but there is no evidence that corticosteroids reduce neurological morbidity and many children develop progressive brain pathology during TBM treatment, despite corticosteroid inclusion [2, 3]. Moreover, corticosteroids are ineffective in reducing cerebrospinal fluid tumor necrosis factor α (TNF-α), the key cytokine involved in the inflammatory response of childhood TBM and a potential major driver of adverse outcomes that occur despite adequate mycobacterial killing [6].

The use of anti–TNF-α agents is a promising approach to limit TNF-α–mediated immunopathology in children with TBM. Recently, 2 case series reported favorable treatment outcomes with infliximab, a monoclonal TNF-α antibody, in childhood and adult patients with TBM in whom the disease course was complicated by paradoxical reactions refractory to steroid treatment [7, 8]. Thalidomide, another anti–TNF-α agent, has also shown encouraging results from observational studies when used at low doses in children with TBM complications [9]; this drug was given in 8.6% of patients in Thee et al study [1]. Prospective clinical trials are warranted to assess the efficacy and safety of these drugs for severe paradoxical reactions, but potentially also for TBM in general given the frequency of severe immune-mediated sequelae (mainly, irreversible stroke resulting from cerebral vasculitis) and the poor neurological outcomes achieved with standard treatment [3, 10].

When accompanied with effective antimicrobial therapy, we believe that suppressing TNF-α–mediated inflammation has the potential to reduce long-term neurological sequelae. Additional studies on the value of high-dose aspirin for treatment of cerebral vasculitis, and other new or repurposed host-directed therapies based on new knowledge from pathogenesis studies, are also warranted [3].

It is clear that improved childhood TBM treatment outcomes require optimization of both antimicrobial and anti-inflammation treatment, with optimal rifampicin and other anti-TB drug dosing and consideration of immunomodulatory treatment beyond corticosteroids.

Notes

Financial support. F. G. was supported by the University of Groningen through the Indonesia Endowment Fund for Education Scholarship (Indonesia Endowment for Education Scholarship [LPDP]; 201711220412046) during the conduct of the study.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Fajri Gafar,[1] Ben J. Marais,[2,3] Heda M. Nataprawira,[4] and Jan-Willem C. Alffenaar[3,5,6]

[1]University of Groningen, Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, -Epidemiology and -Economics, Groningen, The Netherlands; [2]The Children's Hospital at Westmead, Sydney, New South Wales, Australia; [3]University of Sydney Institute for Infectious Diseases, Sydney, New South Wales, Australia; [4]Division of Pediatric Respirology, Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital, Bandung, Indonesia; [5]School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; and [6]Westmead Hospital, Sydney, New South Wales, Australia

References

1. Thee S, Roy RB, Blázquez-Gamero D, et al. Treatment and outcome in children with tuberculous meningitis: a multicentre Paediatric Tuberculosis Network European Trials Group study. Clin Infect Dis **2021**:ciab982. doi:10.1093/cid/ciab982
2. Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis **2014**; 14:947–57.

3. Huynh J, Thwaites G, Marais BJ, Schaaf HS. Tuberculosis treatment in children: the changing landscape. Paediatr Respir Rev **2020**; 36:33–43.
4. World Health Organization. Rapid communication on updated guidance on the management of tuberculosis in children and adolescents. Geneva, Switzerland: World Health Organization, **2021**. Available at: https://www.who.int/publications/i/item/9789240033450. Accessed 30 October 2021.
5. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics **1997**; 99:226–31.
6. Donald PR, Schoeman JF, Beyers N, et al. Concentrations of interferon γ, tumor necrosis factor α, and interleukin-1β in the cerebrospinal fluid of children treated for tuberculous meningitis. Clin Infect Dis **1995**; 21:924–9.
7. Abo Y-N, Curtis N, Osowicki J, et al. Infliximab for paradoxical reactions in pediatric central nervous system tuberculosis. J Pediatric Infect Dis Soc **2021**:piab094. doi:10.1093/jpids/piab094
8. Marais BJ, Cheong E, Fernando S, et al. Use of infliximab to treat paradoxical tuberculous meningitis reactions. Open Forum Infect Dis **2021**; 8:ofaa604.
9. Van Toorn R, Solomons RS, Seddon JA, Schoeman JF. Thalidomide use for complicated central nervous system tuberculosis in children: insights from an observational cohort. Clin Infect Dis **2021**; 72:e136–45.
10. Hill J, Marais BJ. Improved treatment for children with tuberculous meningitis—acting on what we know. Arch Dis Child. **2022**; 107:68–9.

Correspondence: F. Gafar, University of Groningen, Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, -Epidemiology and -Economics, Antonius Deusinglaan 1 (room 3214.0450), 9713 Av Groningen, The Netherlands (f.gafar@rug.nl, or fajri.gafar@gmail.com).

Clinical Infectious Diseases® 2022;75(2):360–1

https://doi.org/10.1093/cid/ciab1036