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References

1. Velásquez GE, Brooks MB, Coit JM, Pertinez H, Vargas Vásquez D, Sánchez Garavito E, *et al*. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis: a randomized controlled trial. *Am J Respir Crit Care Med* 2018;198:657–666.
2. Aarnoutse RE, Kibiki GS, Reither K, Semvua HH, Haraka F, Mtabho CM, *et al*. Pharmacokinetics, tolerability, and bacteriological response of rifampin administered at 600, 900, and 1,200 milligrams daily in patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 2017; 61:e01054-17.
3. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, *et al*.; PanACEA Consortium. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015;191:1058–1065.
4. Svensson RJ, Svensson EM, Aarnoutse RE, Diacon AH, Dawson R, Gillespie SH, *et al*. Greater early bactericidal activity at higher rifampicin doses revealed by modeling and clinical trial simulations. *J Infect Dis* 2018;218:991–999.
5. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, *et al*.; PanACEA Consortium. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017;17: 39–49.
6. Svensson EM, Svensson RJ, Te Brake LHM, Boeree MJ, Heinrich N, Konsten S, *et al*. The potential for treatment shortening with higher rifampicin doses: relating drug exposure to treatment response in patients with pulmonary tuberculosis. *Clin Infect Dis* 2018;67:34–41.

Reply to te Brake *et al.*

From the Authors:

We thank te Brake and colleagues for their interest in the HIRIF (Evaluation of High-Dose Rifampin in Patients with New, Smear-Positive Tuberculosis) trial results (1, 2) and for the PanACEA (Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics) consortium's ongoing commitment to optimize rifampin dosing for patients with tuberculosis. te Brake and colleagues highlight a perceived difference between the HIRIF findings and those of HIGHRIF2 (PanACEA HIGHRIF study 2) (3). The direction and magnitude of the effects observed in both trials were similar: HIGHRIF2 showed a nonsignificant trend toward a higher hazard of culture conversion in both mycobacteria growth indicator tube and Löwenstein-Jensen medium for the 1,200 mg dose compared with the 600 mg dose, and HIRIF revealed that higher rifampin doses and exposure resulted in modest and statistically significant increases in the rate of sputum culture sterilization (2). Interpretation of the two studies is consistent: rifampin doses up to 20 mg/kg/d, with no additional changes to the regimen, are unlikely to permit treatment shortening.

Similarly to HIGHRIF2, HIRIF found no difference in the secondary efficacy outcome of 8-week culture conversion in Löwenstein-Jensen medium with daily rifampin doses up to 20 mg/kg. Rifampin doses also did not influence the frequency of treatment failure and disease recurrence at 12 months. HIRIF was not powered for these secondary endpoints, which would have required a much larger sample size than was possible for a phase II trial. We are encouraged by the advances the PanACEA consortium has made to date in optimizing doses of rifampin higher than 20 mg/kg/d. We also look forward to improving the statistical power for efficacy and safety evaluations by pooling HIRIF and HIGHRIF2 data through collaboration with the authors of the correspondence. Combined with ongoing trials to optimize the dose of rifampin, pooled individual-level patient data analyses will be critical to influence future treatment guidelines and improve the lives of patients with tuberculosis. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Supported by National Institute of Allergy and Infectious Diseases/NIH grants U01 AI091429 (C.D.M. and G.R.D.) and L30 AI120170 and UM1 AI068636 (G.E.V.). G.E.V. received support from the Ronda Stryker and William Johnston Fellowship in Global Health and Social Medicine and the Dr. Lynne Reid/Drs. Eleanor and Miles Shore Fellowship at Harvard Medical School, the Burke Global Health Fellowship at the Harvard Global Health Institute, and the AIDS Clinical Trials Group Minority HIV Investigator Mentoring Program. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or the institutions with which the authors are affiliated.

Originally Published in Press as DOI: 10.1164/rccm.201812-2281LE on January 15, 2019

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References

1. Peloquin CA, Velásquez GE, Lecca L, Calderón RI, Coit J, Milstein M, *et al*. Pharmacokinetic evidence from the HIRIF trial to support increased doses of rifampin for tuberculosis. *Antimicrob Agents Chemother* 2017;61:e00038-17.
2. Velásquez GE, Brooks MB, Coit JM, Pertinez H, Vargas Vásquez D, Sánchez Garavito E, *et al*. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis: a randomized controlled trial. *Am J Respir Crit Care Med* 2018;198:657–666.
3. Aarnoutse RE, Kibiki GS, Reither K, Semvua HH, Haraka F, Mtabho CM, *et al*.; PanACEA Consortium. Pharmacokinetics, tolerability, and bacteriological response of rifampin administered at 600, 900, and 1,200 milligrams daily in patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 2017;61:e01054-17.

Obstructive Sleep Apnea and Cognitive Decline in Older Adults

To the Editor:

Gosselin and colleagues conducted a systematic review of the association between obstructive sleep apnea (OSA) and cognitive decline in older adults with special reference to aging, neurodegenerative mechanism in the brain, treatment effect, and future perspective (1). Although the content of this summary report is valid, I would like to add serum insulin and insulin activity in the brain, which seems indispensable for understanding the biological mechanism of cognitive decline in older adults.

Kullmann and colleagues investigated the effect of three doses of insulin as nasal sprays on the central and autonomous nervous systems (2). Although high-dose nasal insulin showed spillover into the bloodstream, nasal insulin dose-dependently modulated regional brain activity and normalized the high-frequency component of heart rate variability. Insulin activity in the brain is inversely related to serum insulin levels (3), and metabolic disorders caused by insulin resistance with hyperinsulinemia would be indirectly related to OSA and cognitive decline.

Rodríguez-Flores and colleagues investigated the association between obesity and the breath-holding index, which was measured by transcranial Doppler as an indicator of vasomotor reactivity of the brain (4). Subjects without diabetes mellitus and hypertension were selected, and there was a linear negative association between obesity and the breath-holding index, which was adjusted by insulin resistance. The authors concluded that insulin resistance made no contribution to the association between obesity and vasomotor reactivity of the brain, although obesity was closely associated with insulin resistance. There is a significant relationship between OSA and vasomotor reactivity of the brain, and the interrelationship among OSA, cognitive impairment, and depression should be comprehensively evaluated (5).

Lal and colleagues explored biomarkers of cognitive impairment in female patients with OSA who were 45–60 years of age (6). Pathway analysis showed that serum insulin was a prominent protein for regulating other significant biomarkers. In addition, advanced stages of cognitive impairment, such as Alzheimer's disease, presented similar findings. Taken together, serum insulin and insulin in the brain might be one of the predictors of cognitive decline. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Gosselin N, Baril AA, Osorio RS, Kaminska M, Carrier J. Obstructive sleep apnea and the risk of cognitive decline in older adults. *Am J Respir Crit Care Med* 2019;199:142–148.
2. Kullmann S, Veit R, Peter A, Pohmann R, Scheffler K, Häring HU, *et al*. Dose-dependent effects of intranasal insulin on resting-state brain activity. *J Clin Endocrinol Metab* 2018;103:253–262.
3. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res* 2007;4:147–152.
4. Rodríguez-Flores M, García-García E, Cano-Nigenda CV, Cantú-Brito C. Relationship of obesity and insulin resistance with the cerebrovascular reactivity: a case control study. *Cardiovasc Diabetol* 2014;13:2.
5. Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. *Am J Geriatr Psychiatry* 2016;24:496–508.

Originally Published in Press as DOI: 10.1164/rccm.201811-2173LE on January 16, 2019