Tolerability of rifapentine-based regimens in latent tuberculosis infection treatment in the elderly

To the Editor:

Management of latent tuberculosis infection (LTBI) is a core intervention in the pursuit of tuberculosis (TB) elimination and is one of the eight activities recommended by the World Health Organization [1]. We read with great interest the paper by Gao *et al.* [2] investigating two short-course regimens with rifapentine plus isoniazid for the treatment of LTBI in Chinese patients aged 50–70 years. They reported that due to the ever-increasing occurrence of adverse events, the 3-month once-weekly regimen and the 2-month twice-weekly regimen were truncated to 8 and 6 weeks, respectively. Gao *et al.* [2] concluded that the short regimens tested must be used with caution among the elderly because of a high frequency of adverse events. The findings reported by Gao *et al.* [2] were not consistent with our experience in Taiwan.

The use of 3-month once-weekly rifapentine plus isoniazid (3HP) for the treatment of LTBI in Taiwan began with two pilot studies that enrolled contacts of TB patients [3, 4]. Subsequently, the LTBI Treatment for All Contacts Program was initiated in 2016, providing 3HP as well as 9-month-isoniazid (9H) for the treatment of LTBI among contacts aged 12 years or older with directly observed preventive therapy. 3HP was endorsed by the Taiwan Centers for Disease Control [5], although at that time rifapentine was not yet approved by the Taiwan Food and Drug Administration [6].

We closely monitored adverse events and reasons for the discontinuation of LTBI treatment were entered into the electronic TB case management system by public health nurses. Serious adverse events were defined as any hospitalisation, emergency department visit for more than 24 h or death during treatment. We reviewed case management records and medical charts to estimate serious adverse events associated with 3HP using the Modified Naranjo Adverse Drug Reaction Probability Scale [7].

Between April 2016 and June 2018, a total of 14 676 individuals received treatment of LTBI, of whom 7974 (54%) were aged 50 years or older. Of the 7974 individuals, 5087 (63.8%) preferred 3HP and 2887 preferred 9H. The proportion of individuals with early termination of treatment due to adverse events in those who were treated with 3HP was lower than that with those treated with 9H (8.0% (409/5087) *versus* 9.4% (272/2887); p=0.03). The most frequently encountered adverse events leading to permanent discontinuation differed between the two regimens. Among patients who terminated 3HP early, 30% discontinued treatment due to fever; among patients who terminated 9H early, 53% discontinued due to drug-induced hepatitis. 85 (0.84%) patients treated with 3HP had serious adverse events and permanently discontinued 3HP, mainly due to flu-like illness (53%), hypersensitivity (24%) and hepatotoxicity (18%). No death or long-term sequelae associated with 3HP was observed.

We analysed completion of LTBI treatment among 4172 individuals aged 50 years and older who had LTBI treatment initiated between April 2016 and July 2017 (table 1). Those who received 3HP had a higher treatment completion rate compared to those receiving 9H (83.9% *versus* 78.8%; p<0.001). Gao *et al.* [2] reported that 1% of those who received 3HP had drug-induced hepatotoxicity leading to permanent discontinuation of treatment after 8 weeks. This figure was found to be 0.8% in our study cohort and no fulminant hepatic failure was noted.

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TABLE 1 Treatment outcome of latent tuberculosis infection for those aged 50 years and older

	3HP	9H	p-value
Total subjects	2348 (100%)	1824 (100%)	
Males	1129 (48.1%)	839 (46.0%)	0.181
Age <75 years	2054 (87.5%)	1314 (72.0%)	<0.001
Treatment completed	1971 (83.9%)	1438 (78.8%)	<0.001
Any adverse event leading to permanent discontinuation of treatment	281 (12.0%)	172 (9.4%)	0.009
Hepatotoxicity leading to permanent discontinuation of treatment	18 (0.8%)	35 (1.9%)	0.001

Total n=4172. p-values are calculated using the Chi-square test. 3HP: 3-month once-weekly rifapentine plus isoniazid; 9H: 9-month isoniazid.

Drug quality may be associated with adverse events. Currently, isoniazid used in Taiwan is generic and is domestically produced by pharmaceutic companies with good manufacturing practice following a pharmaceutical inspection co-operation scheme. Rifapentine (Priftin) was purchased from Sanofi produced in Italy. Since the study was discontinued early, we wonder to what extent a high frequency of adverse events observed by GAO *et al.* [2] were due to the drugs that they used among rural residents in Zhongmu County, China. Furthermore, tolerability of treatment of LTBI could be relatively low because the subjects in Zhongmu did not have clinical symptoms as severe as hepatic failure. GAO *et al.* [2] did not use 9H and were not able to assess tolerability of 9H in their study population. Thus, it is not clear to what extent tolerability of LTBI treatment itself has contributed to the challenge of completing 3HP treatment.

It has been reported that age is associated with adverse events and the elderly are more likely to experience adverse events during the treatment of LTBI, regardless of the regimens used [4, 8]. However, our experience has shown that with proper support and medical care under programmatic conditions, it is feasible to achieve a high completion rate of 3HP, even among the elderly [4, 9]. Treatment of LTBI among the elderly to mitigate the risk of developing active TB is crucial in settings where TB burden is disproportionally high among the elderly [10]. Our experience shows that the use of 3HP for the treatment of LTBI is a useful tool for achieving the goals of the "The End TB Strategy" and, hopefully, in eliminating TB.

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Reference

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