Correspondence

Lack of a Therapeutic Role for Interferon \( \gamma \) in Patients With Tuberculosis

To the Editor—I read with interest the recent article by Wong and Jacobs on the effects of interferon \( \gamma \) (IFN-\( \gamma \)) on Mycobacterium tuberculosis–infected macrophages [1]. I believe their findings are an important contribution to our understanding of the human biology of M. tuberculosis infection. However, I must take issue with their speculation that their findings indicate it is very unlikely that IFN-\( \gamma \) will have any future therapeutic role in patients with tuberculosis without overt defects in its production.

As the authors noted, the first trial of therapeutic IFN-\( \gamma \) in patients with tuberculosis without overt defects in IFN-\( \gamma \) production or responsiveness was reported by Condos et al in 1997 [2]. In that uncontrolled study, aerosolized IFN-\( \gamma \) 500 \( \mu \)g thrice weekly was added to the current therapy for 5 patients with multidrug-resistant tuberculosis. The study found that results of sputum smears became negative and that the number of colony-forming units tended to decrease. However, none of 2 small uncontrolled and 2 adequately powered controlled subsequent trials has been successful in replicating those results (Table 1). The most rigorous trial, conducted by InterMune, compared aerosolized IFN-\( \gamma \) 500 \( \mu \)g thrice weekly for 6 months to placebo in 80 patients with multidrug-resistant tuberculosis, all of whom also received standardized therapy with second-line drugs [6]. The study design included an aerosolized placebo. The study was halted prematurely by its external safety monitoring board because of a trend toward increased mortality in the experimental arm (10 deaths, compared with 5 in the control arm; \( P = .14 \)), with no beneficial effect on sputum smear or culture results or chest radiography findings. The study findings have never been formally published but are described in an online supplement that accompanies the article by Dawson et al [5].

The only published randomized controlled trial of adjunctive IFN-\( \gamma \) in tuberculosis compared the effects of standard therapy plus IFN-\( \gamma \) 200 \( \mu \)g given thrice weekly for 4 months by aerosol or by subcutaneous injection with the effects of standard therapy alone in 77 evaluable patients with drug-susceptible pulmonary tuberculosis [5]. All subjects also received standard 4-drug tuberculosis therapy. The study design did not include a subcutaneous or aerosolized placebo. The analysis of the study’s primary end points (ie, times to sputum smear and culture conversion) as it was reported differed from that described in the study’s statistical analysis plan, because results of the subcutaneous IFN-\( \gamma \) and control arms were merged and because the planned intent-to-treat analysis was abandoned. Sputum smear findings were reported out to 120 days. A transient beneficial effect of aerosolized treatment on sputum smear results was noted at 4 weeks, but it was absent at all subsequent time points. A sputum culture conversion rate of 32% was reported at 4 weeks in the aerosolized IFN-\( \gamma \) arm, compared with 18% in the other arms combined (\( P = .15 \)), but no subsequent data were provided. Sputum culture status at 2 months has recognized prognostic value in the evaluation of new tuberculosis regimens [7]. In contrast, sputum smear has no recognized prognostic value, nor does any sputum parameter at 1 month [8, 9].

Subsequent research has found that most IFN-\( \gamma \)-induced genes are already up-regulated in the lung during tuberculosis and that therapeutic aerosolized IFN-\( \gamma \) has relatively little additional effect [10]. These findings indicate it is very unlikely that IFN-\( \gamma \) will have any future therapeutic role in patients with tuberculosis without overt defects in its production.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has 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.

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References

Table 1. Clinical Trials of Adjunctive Interferon-γ (IFN-γ) in Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Arm(s)</th>
<th>Control Arm</th>
<th>Microbiologic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condos et al [2]</td>
<td>Subjects, no. 5</td>
<td>IFN-γ Regimen 500 µg aerosol 3 times/wk for 1 mo</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Suarez-Mendez et al [3]</td>
<td>Subjects, no. 5</td>
<td>1 MU intramuscularly daily, then 3 times/wk for 6 mo</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Koh et al [4]</td>
<td>Subjects, no. 6</td>
<td>IFN-γ Regimen 2 MU aerosol 3 times/wk for 6 mo</td>
<td>Not applicable</td>
</tr>
<tr>
<td>InterMunea</td>
<td>Subjects, no. 40</td>
<td>IFN-γ Regimen 500 µg aerosol 3 times/wk for 6 mo</td>
<td>40 Aerosolized placebo</td>
</tr>
<tr>
<td>Dawson et al [5]</td>
<td>Arm 1, 28</td>
<td>IFN-γ Regimen Arm 1, 200 µg aerosol 3 times/wk for 4 mo Arm 2, 200 µg subcutaneously 3 times/wk for 4 mo</td>
<td>26 No aerosolized or subcutaneously administered placebo</td>
</tr>
</tbody>
</table>

* The InterMune study was halted prematurely by its safety monitoring board because of a trend in the experimental arm toward excess deaths without corresponding microbiologic benefit. Its findings have been published only as an online supplement to the article by Dawson et al [5].