Chaperonin 10 is a highly conserved protein that is essential in protein folding. Recombinant chaperonin 10 (Cpn10) (1 amino acid different to native chaperonin 10) and has immunomodulatory function in vitro and in vivo. Treatment with Cpn10 improved clinical disease activity in patients with rheumatoid arthritis and downregulated cytokine responses of immune cells to cellular stimuli. An exploratory study of Cpn10 treatment for chronic plaque psoriasis is reported.

Methods. Forty patients were screened, and 24 (aged 18 to 75 years) with plaque psoriasis for at least 6 months prior to screening, 10% or greater of the body surface area affected by plaque psoriasis, a Psoriasis Area and Severity Index (PASI) score of 12 or higher (severe psoriasis), and a Physician’s Global Assessment (PGA) score of at least moderate at screening despite current therapies were selected. Patients taking psoriasis medications were eligible if the regimen they had been following was a stable systemic dose for 28 days or longer prior to treatment with Cpn10 or 14 days or longer with topical dosing. Exclusion criteria were infections, malignant neoplasms, abnormal hematologic, renal, or liver function test findings, and treatment with any anti–tumor necrosis factor agent or immunosuppressive drugs within 28 days of starting Cpn10 treatment. In this single-center, double-blind study, patients were randomized into 5-, 7.5-, and 10-mg treatment groups of Cpn10 (XToll; CBio Limited, Brisbane, Australia) that was given intravenously twice weekly for 12 weeks. Outcomes were PASI and PGA scores and the percentages of patients with at least a 50%, 75%, or 90% improvement in PASI scores (PASI 50, PASI 75, and PASI 90). In vitro peripheral blood mononuclear cell reactivity to lipopolysaccharide stimulation was measured by cytokine production. Safety was assessed by physical examination, adverse event profile, laboratory parameters, and vital signs.

Results. Patients with severe plaque psoriasis showed improvement in disease activity in all dose groups. Median percent change in PASI scores (baseline median, 23.9) decreased by day 14 (P = .01) and further by day 84 (P = .02) in the 10-mg group (Figure, A). Improvement was maintained 4 weeks (P = .03) after cessation of Cpn10 treatment. The PGA (baseline median, 4) showed improvement by day 56 (P = .02) with 10 mg (Figure, B) and continued to improve to days 84 (P = .03) and 112 (P = .03). An almost clear PGA rating was achieved in 3 patients in the 10-mg group. All groups demonstrated a PASI 50 and PASI 75 (Table; Figure, C). A PASI 90 was observed in one patient in the 7.5-mg group on days 56 and 70 and in another patient in the 10-mg group on day 70. No difference was seen in between the dose groups at day 84 in the percentage of patients exhibiting a PASI 75 response (P = .08). Peripheral blood mononuclear cells isolated from patients after treatment with Cpn10 produced significantly less TNF-α (day 28, P = .046; day 56, P = .04) (baseline median, 1397 pg/mL) and interleukin 1B (day 28, P = .046; day 56, P = .03) (baseline median, 2567 pg/mL) in the 10-mg group (Figure, D). The most common adverse event was exacerbation of psoriasis (4 cases during the study and 3 cases after the final dose). Decreased lymphocyte counts were observed in 6 patients, 2 of whom had upper respiratory tract infections. One patient was lymphopenic at screening, possibly associated with concomitant sarcoidosis. One patient with diabetes mellitus experienced loss of consciousness judged to be unrelated to the study drug. Three adverse events were rated as probably treatment related (scotoma, psoriasis flare, increased proteinuria). Four patients showed a 4-fold increase in antibody titer to Cpn10. The rel-
evance for efficacy is unknown as clinical improvement in these patients was seen.

Comment. This exploratory study shows preliminary evidence of short-term efficacy and safety and decreased release of TNF-α and interleukin 1β, which is noteworthy in inflammation. Lack of placebo is an acknowledged limitation of this pilot study as marked placebo effects are observed in psoriasis studies. Nevertheless, short-term Cpn10 treatment led to rapid reduction in disease parameters in accord with our earlier observations of disease-modifying activity in chronic inflammatory processes. These results will guide the design of a definitive placebo-controlled study and they raise the possibility that Cpn10 may regulate inflammation in a range of therapeutic areas.

Figure. Change in clinical outcome measures with recombinant chaperonin 10, at a dose of 10 mg twice weekly for 12 weeks. A, Change in Psoriasis Area Severity Index (PASI) score. B, Change in Physician Global Assessment (PGA) score. C, Percentage of patients achieving a 50% or greater improvement in PASI score (PASI 50) or a 75% or greater improvement in PASI score (PASI 75). D, Change in cytokine production by patient-derived peripheral blood mononuclear cells. The error bars in A, B, and D show 95% confidence intervals. *P < .05 (Wilcoxon-signed rank test). TNF-α indicates tumor necrosis factor α; IL-1β, interleukin 1β. Screen refers to a baseline measurement; it was performed 7 ± 2 days prior to the first dose (day 0). Follow-up assessment was performed on day 112 of the trial, 4 weeks after dosing had stopped.

Table. Primary and Secondary Measures of Efficacy of Chaperonin 10 by Dose

<table>
<thead>
<tr>
<th>PASI Response Score</th>
<th>Day</th>
<th>5-mg Dose</th>
<th>7.5-mg Dose</th>
<th>10-mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>84</td>
<td>4 (50) [15.7-84.3]</td>
<td>2 (25) [3.2-65.1]</td>
<td>6 (75) [34.9-96.8]</td>
</tr>
<tr>
<td>75</td>
<td>84</td>
<td>1 (12.5) [0.3-52.6]</td>
<td>1 (12.5) [0.3-52.6]</td>
<td>4 (50) [15.7-84.3]</td>
</tr>
<tr>
<td>90</td>
<td>70</td>
<td>0 [0-36.9]</td>
<td>1 (12.5) [0-52.6]</td>
<td>1 (12.5) [0.3-52.6]</td>
</tr>
</tbody>
</table>

Abbreviation: PASI, Psoriasis Area Severity Index (90, 90% or greater improvement in PASI; 75, 75% or greater improvement; 50, 50% or greater improvement).
is a consultant to CBio Limited and has received stock options from CBio Limited. Drs Hall, McCormack, and Foley were paid by the sponsor to implement the study. There are no further disclosures from any author regarding expert testimony, grants patents, patent applications, or royalties.

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COMMENTS AND OPINIONS

Sentinel Node Biopsy: Facts to Clear the Alleged Clouds

Sentinel node biopsy (SNB) was developed to identify the 20% of patients with intermediate-thickness primary melanoma (1.2-3.5 mm) and regional nodal metastasis who might benefit from lymphadenectomy before, rather than after, clinical nodal recurrence.1 Our group’s randomized international study of the diagnostic utility and prognostic significance of SNB2 was unjustly criticized by González.3 His commentary wrongly claims that our abstract did not include overall results. Although it is not customary to expect survival benefits for a staging and/or diagnostic procedure,4,5 we reported the overall impact of SNB on survival. Our group clearly states in the abstract2(p1307) that the mean estimated 5-year disease-free survival was 78.3% with SNB vs 73.1% with observation (hazard ratio, 0.74; P = .009). Five-year melanoma-specific survival rates were 87.1% and 86.6%, respectively.

González3 wrongly declares that potential bias was introduced by not including SNB patients with nodal recurrence in a survival analysis of all patients with nodal metastases. Our report states in 2 places6,7,8,9 that patients with negative findings from SNB underwent delayed lymphadenectomy for nodal recurrence. Their survival was similar to that of observed patients who developed nodal recurrence (Figure) (subgroup 3 vs subgroup 4; P = .60). However the 5-year melanoma-specific survival rate was 66.2% for all SNB patients with nodal metastases (including those with nodal recurrence) com-