Safety and efficacy of the monoclonal anti–interleukin-5 antibody SCH55700 in the treatment of patients with hypereosinophilic syndrome

Amy D. Klion, Melissa A. Law, Pierre Noel, Yae-Jean Kim, Thomas P. Haverty, and Thomas B. Nutman

Four patients with hypereosinophilic syndrome (HES) refractory to or intolerant of treatment with conventional therapy were treated with a single 1 mg/kg dose of SCH55700. SCH55700 was extremely well tolerated. Two of the 4 patients responded with a fall in eosinophil counts to within the normal range within 48 hours of receiving the drug, accompanied by marked improvement in clinical signs and symptoms. Response was not predicted by serum interleukin-5 (IL-5) levels or presence of the FIP1L1/PDGFRα mutation. Eosinophil counts remained suppressed for up to 12 weeks after treatment; however, exacerbation of symptoms and eosinophilia above baseline levels occurred as drug levels waned. Reinstitution of treatment with monthly SCH55700 led to decreased eosinophilia and symptomatic improvement, albeit to a lesser degree than that seen after the initial dose. These data suggest that anti–IL-5 therapy may be useful in the treatment of HES irrespective of the underlying etiology, although the observed rebound eosinophilia and attenuation of response require further study. (Blood. 2004;103:2939-2941)
baseline, one month after treatment, and prior to the last dose of SCH55700 in patients receiving monthly dosing.

The study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board, and informed consent was obtained from all study participants.

Results and discussion

SCH55700 was extremely well tolerated. One patient complained of transient long-bone pain occurring 6 to 12 hours after the first and second infusions of SCH55700 that was similar in nature to what she had experienced previously with acute lowering of her eosinophil count with steroids. A low-grade fever and upper respiratory symptoms occurred within 3 days of the drug infusion on 2 separate occasions in a single patient and resolved without treatment. In both instances, other members of the patient’s family were ill with similar symptoms. No other adverse effects were reported.

Patients 1 and 2 experienced a rapid decrease in eosinophilia in response to SCH55700 (Figure 1A) accompanied by marked

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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Clinical manifestations</th>
<th>Therapy Baseline eosinophil count, x 10^9/L</th>
<th>Serum IL-5 level, ng/mL</th>
<th>Bone marrow biopsy cellularity, %</th>
<th>Granulocytic precursors in bone marrow aspirate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>52</td>
<td>Mucosal ulcerations, dermatitis, splenomegaly</td>
<td>P, HU, IFN HU 3.630 Yes 2 &lt; 1.95 3.3 70 50 30 58 68 76</td>
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<tr>
<td>2</td>
<td>F</td>
<td>32</td>
<td>Angioedema, dermatitis, myoedema, arthralgias, myalgias</td>
<td>P, HU, IFN P 2.620 No 2 &lt; 1.95 6.1 55 60 60 80 70 78</td>
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<td></td>
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<tr>
<td>3</td>
<td>M</td>
<td>38</td>
<td>Mucosal ulcerations, dermatitis, anemia, thrombocytopenia, splenomegaly</td>
<td>P, HU, IFN P, HU IFN 6.133 Yes &lt; 1.95 &lt; 1.95 &lt; 1.95 95 95 NA ND 41 NA</td>
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</tr>
<tr>
<td>4</td>
<td>F</td>
<td>47</td>
<td>Pericarditis, pleuritis, urticaria, cerebrovascular accident, digital ulcerations</td>
<td>P, HU, IFN, Im HU 3.209 No 223 14.5 24.4 40 40 NA 61 34 NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P indicates prednisone; HU, hydroxyurea; IFN, interferon-α; NA, not applicable; ND, not done; and Im, imatinib mesylate.

*Normal range of eosinophils, 0 x 10^9/L to 0.750 x 10^9/L (0/mm^3 to 750/mm^3).
†Presence of the FIP1L1/PDGFRα fusion.

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improvement in their symptoms, including resolution of skin rash and mucosal ulcerations (patient 1), angioedema (patient 2), fatigue, myalgias, and arthralgias. The clinical and hematologic response was prolonged, lasting for more than 30 days following the infusion of SCH55700, but was associated with a rebound in the peripheral eosinophil count to levels above the pretreatment baseline and a severe exacerbation of symptoms in both subjects at 6 to 8 weeks after treatment. This rebound was preceded by a rise in serum IL-5 detectable at 1 month after treatment (Table 1).

Patient 3 had neither a decrease in his eosinophil count (Figure 1B) nor improvement in his symptoms following treatment with SCH55700 but experienced a self-limited exacerbation in symptoms and peripheral eosinophilia during weeks 1 to 4 after treatment. Patient 4 experienced a rapid decrease in her peripheral eosinophil count from $3.209 \times 10^9/L$ ($3209/mm^3$) to $1.105 \times 10^9/L$ ($1105/mm^3$) immediately following the infusion of SCH55700; however, her symptoms remained unchanged, and her eosinophil level returned to baseline within 7 days of drug administration (Figure 1B). Of note, this patient (patient 4) was the only subject with increased IL-5 levels at baseline (223 pg/mL). Although her serum IL-5 levels decreased following treatment, they remained detectable (14.5 pg/mL on day 3), suggesting that the dose of SCH55700 may have been inadequate in this patient.

Because of their dramatic response to single-dose therapy, patients 1 and 2 received 5 additional monthly doses of SCH55700 at 1 mg/kg per dose. Although both patients responded to the second dose of SCH55700 with a rapid decrease in eosinophilia (Figure 1C-D) and improvement in symptoms, the magnitude and duration of the improvement in symptoms and eosinophilia lessened with each subsequent dose. Drug levels remained detectable throughout treatment and rose with each infusion, inconsistent with the development of neutralizing antibodies as an explanation for the attenuation of response (Figure 1D). Bone marrow biopsy was performed prior to, at 1 month following treatment, and at the time of the last monthly dose. In contrast to studies in asthma that have demonstrated maturational arrest in the bone marrow following anti–IL-5 therapy,7 no significant changes in bone marrow cellularity or eosinophilia were observed (Table 1). Potential explanations for this discrepancy include differences in the underlying disease being studied (asthma versus HES), the antibodies used (mepolizumab versus SCH55700), the dosing (10 mg/kg versus 1 mg/kg), and the timing of the bone marrow sample (2 weeks versus 4 weeks after infusion).

The present study suggests that SCH55700 may be useful in treating a subset of patients with HES irrespective of the underlying etiology and independent of the presence of detectable serum IL-5 levels. Additional studies are needed to determine optimal dosing as well as the prevalence and mechanisms of the observed rebound eosinophilia and attenuation of response.

Acknowledgments

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References

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