Inhibition of Pulmonary Eosinophilia and Hyperreactivity by Antibodies to Interleukin-5

Abstract

Eosinophils infiltrate into the lungs during asthma and may cause the damage associated with pulmonary inflammation. In allergic animal models, antibodies to interleukin (IL)-5 inhibit pulmonary eosinophilia, tissue damage and hyperreactivity. Sch 55700, a humanized antibody against human IL-5, inhibits eosinophilia in these models with an extended biological duration. On the basis of this dosing regimen and the humanized nature of Sch 55700, it is anticipated that the host response leading to tolerance would be minimized.

Key Words

Interleukin-5
Eosinophils
Asthma
Pulmonary inflammation
Sch 55700

Eosinophils are a major cell type infiltrating into the lungs during asthma and have been implicated in the damage associated with pulmonary inflammation [1]. As one of their actions, steroids inhibit eosinophil infiltration, contributing to their anti-inflammatory effects and their capacity to enhance lung function in patients with asthma. However, steroids have side effects that limit their utility, and other approaches that selectivity block pulmonary eosinophilia without causing generalized immunosuppression could lead to significant therapies for treating the causes of asthma.

Interleukin (IL)-5 is a selective eosinophil effector in humans that enhances eosinophil production and release from bone marrow, chemotaxis, activation and survival [2]. The neutralizing TRFK-5 antibody to IL-5 inhibits eosinophil infiltration into the lung tissue and lavage fluid following allergic challenge in sensitized guinea pigs, mice and monkeys [3, 4, 6]. Inhibition is observed when antibody is administered intraperitoneally (i.p.), intravenously (i.v.) or in-
tramuscularly (i.m.) before or after the allergic challenge. In mice and probably in guinea pigs and monkeys, eosinophil accumulation in the lungs following antigen challenge is suppressed subsequent to inhibition of the release of eosinophils from the bone marrow by the TRFK-5 antibody. Despite the multiplicity of cytokines involved in eosinophil production and activation, the TRFK-5 antibody can totally block eosinophil infiltration in these animal models, indicating that these cytokines must act in series rather than in parallel and that IL-5 is involved in a terminal stage of eosinophil maturation and release. The TRFK-5 antibody can also be administered during established eosinophilia, without causing lung damage that could result from acute local degradation of eosinophils.

Critical to any potential therapy for asthma is the capacity to alter the physiology in these animal models. In the allergic guinea pig and monkey models, the animals’ lungs become hyperresponsive to substance P and histamine, respectively, and this hyperresponsiveness is blocked by treat-

ment with the TRFK-5 antibody prior to the challenge [5]. Although the pulmonary mechanics of mice does not change following allergic challenge, lung damage measured histologically as obstruction in the lumen, epithelial desquamation and erythrocytes in the alveoli is inhibited by treatment with the TRFK-5 antibody.

On the basis of these observations in animals, it would seem possible to treat humans with antibodies to IL-5 to attenuate the lung eosinophilia and the decrement in lung function that occur during asthma. However, the TRFK-5 antibody is a rat monoclonal raised against murine IL-5 that would, most likely, be intensely immunogenic in humans. 39D10 is a rat monoclonal against human IL-5 with a Kd of 53 pM against IL-5, but it should also be immunogenic in humans. We, therefore, constructed a human variant of the 39D10 antibody using CDR grafting technology, resulting in Sch 55700. The variable-region framework is the human group one germ line framework for VL and a consensus of human group three germ line sequences for VH, while the constant region is human γ4/κ. By BIAcore analysis at 37°C, the Kd for human IL-5 is 81 pM, with an association rate constant of 4.9×105 AT1 s⁻¹ and a dissociation rate constant of 3.9×105 s⁻¹. As an indication of bioactivity, the EC50 of Sch 55700 for inhibiting IL-5-induced proliferation of the human erythroleukemic cell line, TF-1, is 45 pM On the basis of both BIAcore kinetics and TF-1 proliferation, Sch 55700 is as potent as 39D10, which is the best that could be expected.

When administered 1 h before challenge to Ascaris-XQ-responsive monkeys, Sch 55700 inhibits lung lavage eosinophilia 75% at a dose of 0.3 mg/kg, i.v. At 0.1 mg/kg, i.v., there is no statistically significant inhibition of eosinophil accumulation. This set of monkeys was not hyperresponsive to histamine, so the effects of Sch 55700 on hyperresponsiveness could not be determined. Six months after this single dose of 0.3 mg/kg of Sch 55700, eosinophil accumulation in response to Ascaris challenge is still inhibited by 75%, which is consistent with the results from the TRFK-5 antibody that is active 3 but not 6 months after a single treatment of 0.3 mg/kg, i.v. in monkeys. In the allergic mouse, Sch 55700 inhibits pulmonary eosinophilia at 1 mg/kg, i.p., and therefore is as potent as 39D10 but 10-fold less potent that TRFK-5.

In summary, antibodies to IL-5 inhibit pulmonary eosinophilia and hyperreactivity in allergic animal models. Sch 55700, a humanized antibody against human IL-5, inhibits eosinophilia in these models with an extended biological duration such that treatment of asthma in humans could
involve widely spaced injections. On the basis of this dosing regimen and the humanized nature of Sch 55700, it is anticipated that the host response leading to tolerance would be minimized, but that hypothesis has yet to be tested in humans.

References