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

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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.

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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-

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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×
10 5 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-sensitive 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


