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Passive immunization with allergen-specific IgG antibodies for treatment and prevention of allergy

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ABSTRACT

IgE antibody-mediated allergies affect more than 25% of the population worldwide. To investigate therapeutic and preventive effects of passive immunization with allergen-specific IgG antibodies on allergy in mouse models we used clinically relevant pollen allergens. In a treatment model, mice were sensitized to the major birch pollen allergen Bet v 1 and to the major grass pollen allergens, Phl p 1 and Phl p 5 and then received passive immunization with rabbit IgG antibodies specific for the sensitizing or an unrelated allergen. In a prevention model, mice obtained passive immunization with allergen-specific rabbit IgG before sensitization. Kinetics of the levels of administered IgG antibodies, effects of administered allergen-specific IgG on allergen-specific IgE reactivity, the development of IgE and IgG responses and on immediate allergic reactions were studied by ELISA, rat basophil leukaemia degranulation assays and skin testing, respectively. Treated mice showed an approximately 80% reduction of allergen-specific IgE binding and basophil degranulation which was associated with the levels of administered allergen-specific IgG antibodies. Preventive administration of allergen-specific IgG antibodies suppressed the development of allergen-specific IgE and IgG_1 antibody responses as well as allergen-induced basophil degranulation and skin reactivity. Our results show that passive immunization with allergen-specific IgG antibodies is effective for treatment and prevention of allergy to clinically important pollen allergens in a mouse model and thus may pave the road for the clinical application of allergen-specific antibodies in humans.

Introduction

IgE-mediated allergy affects more than 25% of the population worldwide and shows a continuously increasing prevalence (Floistrup et al. 2006). Allergen-specific immunotherapy (SIT) is currently the only antigen-specific, disease-modifying treatment of allergy and has long-lasting effects (Shamji and Durham 2011). Since the first reports indicated that SIT induces allergen-specific IgG antibodies which block IgE-mediated inflammation (Cooke et al. 1935; Loveless 1940), it has been shown that SIT-induced allergen-specific IgG also reduces T cell reactivity and boosts of IgE production (Larche et al. 2006). Passive immunization of patients with allergen-specific IgG antibodies has been successfully used so far only in combination with active SIT mainly to reduce the sensitivity of patients but not yet as sole treatment procedure (Bernstein et al. 1979; Bousquet et al. 1987; Muller et al. 1986). It has been also reported that SIT-induced allergen-specific IgG antibodies cross the placenta (Flicker et al. 2009) and may protect the offspring from sensitization (Glovsky et al. 1991). Furthermore, it has been demonstrated that elevated cord blood levels of allergen-specific IgG are associated with less allergy development in children (Jenmalm and Bjorksten 2000).

Experimental studies performed in mice and rats with model antigens such as ovalbumin suggested that prenatal active immunization induces allergen-specific IgG antibodies which protect against allergen-induced sensitization and allergic inflammation in the off-spring (Fusaro et al. 2007; Jarrett and Hall 1983; Polte and Hansen 2008; Polte et al. 2008; Uthoff et al. 2003). There are also experimental animal studies using ovalbumin or goat-anti IgD as immunogens demonstrating that passive administration of specific IgG antibodies may be effective in suppressing allergic sensitization, allergic inflammation and even anaphylactic shock (Moerch et al. 2006; Sehra et al. 2003; Strait et al. 2006; Uthoff et al. 2003).

However, so far no studies have been performed with allergens which are relevant for allergy in humans. Here we used clinically important grass pollen allergens (i.e., Phl p 1, Phl p 5) (Laffer et al. 1994; Vrtala et al. 1993; Westritschnig et al. 2008), the major

Abbreviations: i.n., intranasal; SIT, allergen-specific immunotherapy.

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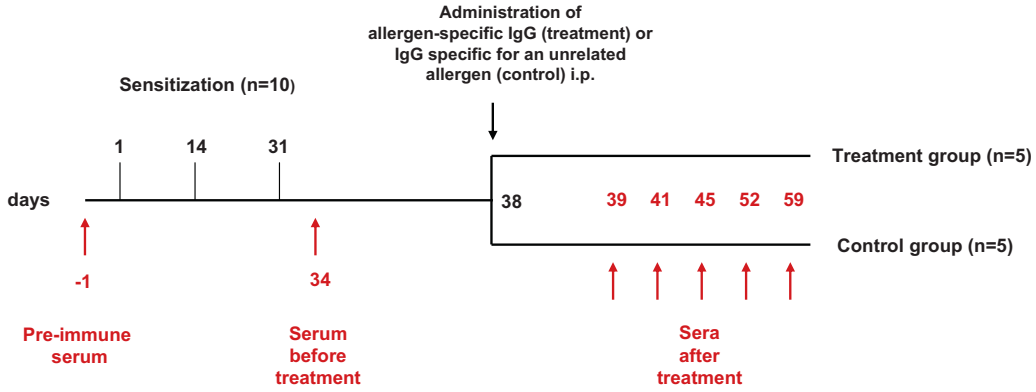

Fig. 1. Scheme of treatment by passive immunization with allergen-specific IgG antibodies. Groups of 10 mice were sensitized three times (days 1, 14 and 31) with aluminium hydroxide-adsorbed allergen and then randomized into two groups ($n = 5$) receiving allergen-specific IgG or IgG specific for an unrelated allergen. Sera were obtained at the time points indicated.

birch pollen allergen Bet v 1 (Breiteneder et al. 1989; Niederberger et al. 1998a,b; Pauli et al. 2008) and corresponding allergen-specific IgG antibodies to investigate whether passive immunization with allergen-specific IgG antibodies can suppress IgE-mediated allergic reactions in a mouse model for treatment. Furthermore, we studied in a preventive mouse model if passive immunization can suppress allergic sensitization.

Materials and methods

Allergens, animals, rabbit immune sera

Purified recombinant allergens (rBet v 1, rPhl p 1, rPhl p 5) were obtained from BIOMAY (Vienna, Austria). Female 6–8 week-old BALB/c mice were purchased from Charles River (Sulzfeld, Germany) and kept in the animal care unit of the Department of Pathophysiology and Allergy Research, Medical University of Vienna according to the local guidelines for animal care. All animal experiments were approved by the Animal Ethics Committee of the Medical University of Vienna and the Austrian Federal Ministry of Science and Research (66009/186-II/10b/2008). Pollen allergen-specific rabbit IgG antibodies were obtained by immunization of rabbits with purified recombinant allergens (rBet v 1, rPhl p 1, rPhl p 5) using complete and incomplete Freund' s adjuvant (CFA, IFA), respectively (Charles River, Kislegg, Germany).

Sensitization and passive antibody treatment of mice

For the therapy model, mice were sensitized by three subcutaneous (s.c.) immunizations (days 1, 14 and 31) with each of the purified recombinant allergens (5 μg/mouse) adsorbed to aluminium hydroxide ($Al(OH)_3$) (Alu-Gel-S; Serva, Ingelheim, Germany) (Fig. 1). Groups of ten mice each were sensitized to rBet v 1, rPhl p 1 or rPhl p 5. Blood samples were taken from the tail veins before sensitization, at day 34 and at days 39, 41, 45, 52 and 59 (Fig. 1). Allergic sensitization was confirmed by the measurement of allergen-specific IgE antibodies at day 34. Mice were then randomized into groups of 5 mice so that mice of each group had comparable allergen-specific IgE levels. Mice in the treatment groups received one intraperitoneal (i.p.) injection of 0.5 ml allergen-specific rabbit IgG whereas mice from the control groups received one i.p. injection of rabbit IgG specific for an unrelated allergen (Fig. 1).

For the preventive model, groups of mice ($n = 5$) received either i.p. 0.5 ml Phl p 5-specific rabbit IgG antibodies (prophylaxis group) or 0.5 ml rabbit IgG antibodies specific for an unrelated allergen, Phl p 2 (control group) on day 0 and, on day 14 (Fig. 2). On day 1 mice of both groups were simultaneously sensitized s.c. with 5 μg rPhl p 5 and 5 μg rBet v 1 adsorbed to aluminium hydroxide ($Al(OH)_3$). Blood was collected from the tail veins before sensitization as well as on days 2, 8 and 20 (Fig. 2).

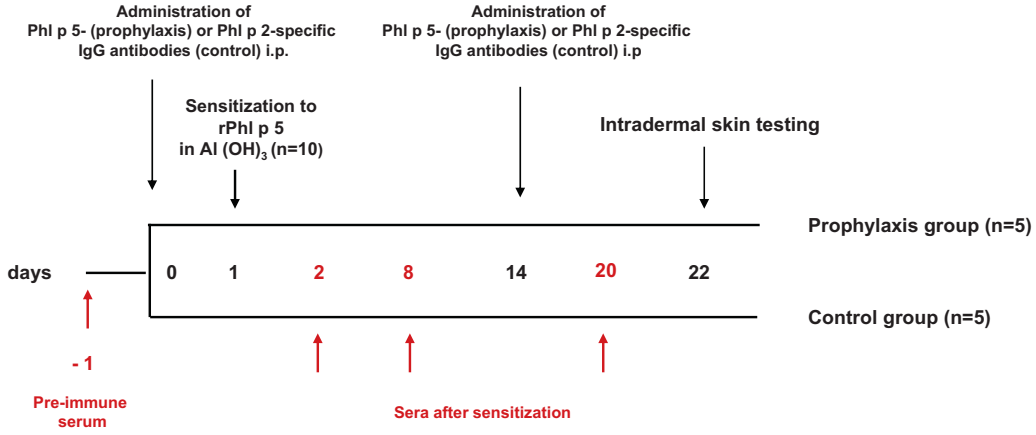

Fig. 2. Scheme for prophylactic administration of allergen-specific IgG antibodies. Mice received Phl p 5-specific IgG (prophylaxis group) or Phl p 2-specific IgG (control group) and were then sensitized to Phl p 5. Bleeding, administration of antibodies and intradermal testing were done at the time points indicated.