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Possible dual role of anti-idiotypic antibodies in combined passive and active immunotherapy in honeybee sting allergy

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Background: Passive infusion of beekeepers' plasma was shown to protect patients against systemic reactions occurring during active immunotherapy by mechanisms still to be clarified. It is tempting to speculate that anti-idiotypic antibodies could play a role because they are found in beekeepers' plasma and are involved in the regulation of IgE synthesis.

Methods: In this report we studied the effects of passive infusion of a beekeeper's plasma rich in anti-idiotypic antibodies to a patient who experienced systemic reactions to honeybee venom.

Results: We reported, during the days after the infusion, a decrease of clinical sensitivity to the honeybee venom. Indeed, the patient tolerated a cumulative dose of 280 µg of venom without adverse reactions. We also observed decreases in skin mast cell and in basophil sensitivity. After the plasma infusion, a modified rush immunotherapy with honeybee venom was initiated in our patient. In the following 76 weeks, increased levels of anti-idiotypic antibodies in the serum of the patient were associated with a diminution of specific antibodies (IgG and IgE) to honeybee venom.

Conclusion: These results suggest a dual role of anti-id in our combined protocol of passive and active immunotherapy: an immediate action on clinical sensitivity along with a decrease of skin mast cell and basophil sensitivity and an immunoregulatory role on specific antibody production. (*J ALLERGY CLIN IMMUNOL* 1994;93:1039-46.)

Key words: Honeybee, venom, immunotherapy, anti-idiotypic, immunoglobulins

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Allergic reactions to Hymenoptera stings range from large local skin lesions (urticaria, pruritus, and angioedema) to systemic reactions involving more than one system (skin, upper and lower respiratory tracts, gastrointestinal tract), which can lead to circulatory collapse (hypotension and shock). Systemic reactions occur in 0.4% to 4% of the population¹⁻³ and result in at least 40 deaths per year in the United States.⁴ In the last two decades, immunotherapy with venom has become available, and it has been shown that immunotherapy at a dose of 100 µg of venom per month

Abbreviations used

aId Abs:	Anti-idiotypic antibodies
BKP:	Beekeeper's plasma
HBV:	Honeybee venom
IgE HBV:	Specific IgE antibodies to honeybee venom
IgG HBV:	Specific IgG antibodies to honeybee venom

provides excellent protection to at least in 95% of patients who are clinically sensitive to bee stings.⁵ However, systemic reactions could occur during immunotherapy, and their incidence varies between 5%⁶ and 50%,^{7, 8} depending on the species of venom used for immunotherapy and the type of schedule used for desensitization. Müller et al.⁹ reported that the incidence of systemic reactions during immunotherapy with honeybee venom (HBV) was more frequent (22%) than that during immunotherapy with yellow jacket venom (3%). Because of the severity and/or the frequency of systemic reactions to HBV, some patients cannot receive sufficient amounts of HBV to achieve protection. Therefore some of these patients were then given infusion of plasma from nonallergic beekeepers (BKP) just before initiation of active immunotherapy.^{8, 10, 11} This procedure was shown to prevent or substantially reduce systemic reactions and permitted patients to receive immunotherapy with between 100 µg and 200 µg of venom without allergic side effects. The mechanisms by which immunotherapy provides protection are complex and still incompletely defined. The increased IgG titers observed after immunotherapy and their correlation with clinical improvement have suggested a role for blocking IgG.^{12, 13} Nevertheless, there are some patients with high antibody titers who are not protected,¹⁴ suggesting that other factors are associated with successful immunotherapy. In patients with pollen rhinitis, immunotherapy was shown to restore the levels of anti-idiotypic antibodies (aId Abs).^{15, 16} These aId Abs are produced during any immune response and are directed against the antigen binding site of the first antibody produced in response to antigen challenge. In animal models aId Abs have been shown to downregulate the IgE antibody response^{17, 18} and to inhibit the antigen-specific human IgE antibody response *in vitro*.¹⁹ These regulatory aId Abs seem to be defective in atopic patients, and it has been speculated that aId Abs transferred by passive immunization or produced during venom immunotherapy could play a role in the protective immu-

nity. Moreover, it is interesting that high levels of aId Abs were found in BKP.²⁰

In this article, we have evaluated a patient who is highly allergic to HBV, who experienced several systemic reactions during desensitization, and for whom the established protective concentration could not be achieved. This patient was transfused with plasma from a nonallergic beekeeper containing aId Abs to reach protective doses of HBV without systemic reactions. The effects of such a plasma on the clinical and immunologic parameters were assessed: clinical response to increasing doses of HBV, sensitivity of skin mast cells and basophils, and levels of specific IgE antibody and IgG antibody to HBV (IgE, IgG HBV). Then active immunotherapy with HBV was initiated, and the presence of aId Abs was correlated with immune parameters associated with successful therapy.

METHODS

Patient and BKP

The patient is a 22-year-old woman who had one anaphylactic reaction to honeybee sting manifested by urticaria, angioedema, severe respiratory distress, nausea, and loss of consciousness. She had positive skin test and RAST results to HBV. During modified rush immunotherapy she had up to 15 systemic reactions requiring emergency treatment, including epinephrine administration. She could not tolerate more than 25 µg of HBV. Plasma (500 ml) was taken from a hyperimmune, nonallergic beekeeper by plasmapheresis at one of the local transfusion centers of the Canadian Red Cross (Québec). The beekeeper is not a member of the patient's family. The plasma tested negative for hepatitis-associated antigens and human immunodeficiency virus. Honeybee sting-sensitive patients and volunteers with no known allergies, no history of honeybee stings, and negative skin test responses to HBV were also included in this study.

Antigens and antibody

HBV for skin testing and immunotherapy was obtained from Pharmacia AB (Uppsala, Sweden), and venom used for affinity purification of anti-HBV antibody was purchased from Sigma Chemical Co. (St. Louis, Mo.).

Anti-HBV antibodies were obtained by immunosorbent technique with HBV fixed on solid phase. γ-Globulins were separated from BKP by precipitation with ammonium sulfate (50%) and passed through HBV coupled to a CL4B Sepharose column (Pharmacia, Piscataway, N.J.). The adsorbed antibodies were then eluted and passed through human IgM and IgG (Chemicon International, Inc., Temecula, Calif.) coupled to CL4B Sepharose to remove Fc-binding rheumatoid factors. The nonadsorbed material was considered as affinity-purified anti-HBV.

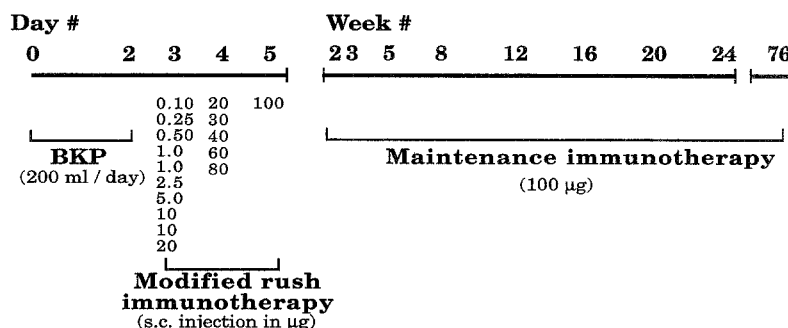


FIG. 1. Schedule of passive and active immunotherapy. BKP was given on 2 consecutive days before initiation of a modified rush immunotherapy regimen.

Skin tests

The patient underwent skin prick testing with four serial 10-fold dilutions of HBV, starting at a concentration of 10 µg/ml. Fifteen minutes after the puncture, wheal reactions were measured, and the dilution (end point) eliciting a wheal reaction equal to that of the reaction of the positive control (histamine, 1 mg/ml, in buffer solution with 50% glycerin) was determined.

HBV-induced basophil histamine release

Histamine release experiments were done as previously described.²¹ Briefly, leukocytes from the patient were isolated by dextran (Pharmacia, Piscataway, N.J.) sedimentation as described by Lichtenstein and Olser.²² The cells (4×10^6 cells/ml) were washed and incubated alone or with various concentrations (1 to 0.0001 µg/ml) of either HBV, anti-IgE monoclonal antibody, or unrelated allergenic ragweed extracts to which the patient was not sensitive, for 45 minutes at 37° C with constant agitation. At the end of this incubation, test tubes were centrifuged at 130g for 5 minutes at 4° C, and the supernatants were collected for subsequent measurement of histamine content by means of a radioenzymatic assay, as previously reported.²³ All values were corrected for spontaneous release, and the percentage of histamine release was calculated on the basis of total cellular histamine content determined after cell disruption by boiling. The results were expressed as percentage of histamine release.

Determination of serum-specific antibodies to HBV

IgG HBV were determined by the Phadebas IgG RAST test, and IgE HBV concentrations were evaluated with Phadenzym RAST (Pharmacia, Uppsala, Sweden).

Detection of aId Abs in sera and plasma

Inhibition of IgE HBV binding to HBV. The presence of aId Abs in the patient's serum or BKP was evaluated by the binding inhibition of Phadebas IgE test. Samples were first depleted of anti-HBV activity by extensive adsorption on an HBV-Sepharose CL4B column and

adsorption on an HBV-Sepharose CL4B column and on nonspecific human immunoglobulins. Patient's serum drawn before the immunotherapy protocol was diluted 1:4 and incubated alone or with idiotype-depleted samples for 30 minutes at 37° C. After this procedure, standard RAST was performed as described earlier. The percentage of binding inhibition was calculated as follows:

$$\% \text{ Inhibition} = \frac{OD_0 - OD_i}{OD_0} \times 100$$

where OD_0 and OD_i represent, respectively, the optical density without and the optical density in the presence of idiotype-depleted samples.

Binding inhibition was also used to verify the presence of cross-reactive idiotype in BKP and serum from patients allergic to HBV. Briefly, sera from seven patients who have clinical history of allergic reactions and positive skin test results to HBV were diluted 1:4 and incubated alone or with various dilutions of BKP depleted on idiotype activity. RAST assay was then carried out as described above.

Determination of aId Abs by immunodot technique. Briefly, γ -globulin fractions of BKP or patient's serum were dotted on nitrocellulose sheets. After saturation of free protein-binding sites, sheets were incubated overnight at 4° C with affinity-purified anti-HBV antibody labeled with iodine 125. After washes, autoradiography was carried out.

Immunotherapy protocol

The antibody protocol is displayed in Fig. 1. Passive immunization was given by intravenous infusion of 400 ml of plasma (200 ml per day on 2 consecutive days). The modified rush immunotherapy was started the day after the second infusion of BKP. HBV was administered in doses of 0.1 µg to 20 µg at 30-minute intervals for the first day. The next day, doses of HBV were increased to reach 80 µg, and finally, the maintenance dose (100 µg) was given in a single injection on the third day. Every month, the patient received a maintenance dose of 100 µg of HBV. Blood samples were drawn for histamine release assays and for measurement of antibody levels.

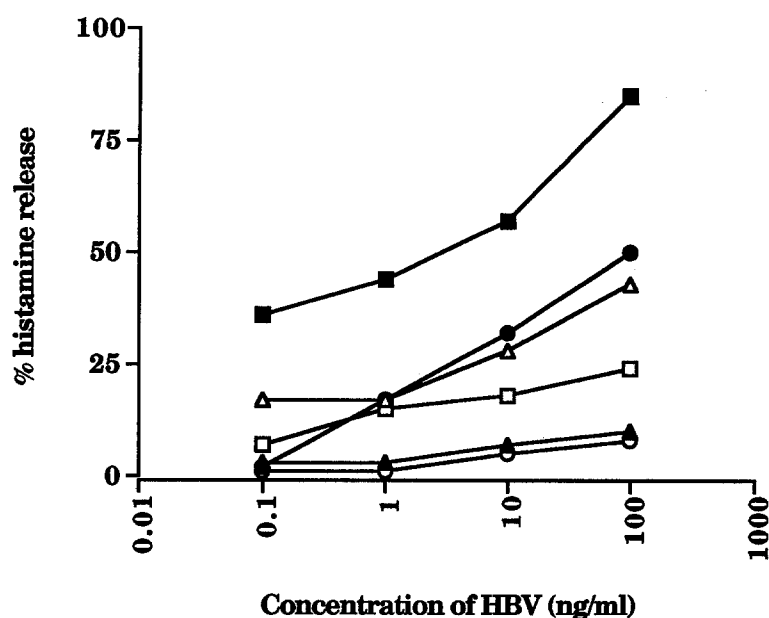


FIG. 2. HBV-induced basophil histamine release of sensitive patient in the course of combined immunotherapy. Basophils from patient were challenged with different concentrations of HBV. Blood samples were drawn at various times during the treatment: day 0 (■), day 3 (△), week 2 (●), week 8 (□), week 24 (▲), and week 76 (○).

TABLE I. Follow-up of specific antibody against HBV during passive and active immunotherapy

	HBV-specific antibody	
	IgG (U/ml)	IgE (PRU/ml)
Patient		
Day 0	320	> 17.5
Day 3	330	> 17.5
Week 2	525	> 17.5
Week 5	ND	> 17.5
Week 8	1080	> 17.5
Week 16	930	> 17.5
Week 20	865	10.3
Week 24	850	5.0
Week 76	550	2.3
Normal subject	20	< 0.35
BKP	3500	< 0.35

All determination of specific IgG or IgE were done on a single occasion. Values represent the mean of triplicate. PRU, Phadebas RAST units; ND, not done.

RESULTS

Clinical parameters

Before initiation of combined passive and active antibody, the skin sensitivity of the patient was 0.1 μ g/ml as determined by an end-point titration skin test. Before infusion of BKP, the patient tolerated no more than 25 μ g of HBV. The day after the passive infusion and before initiation of rush antibody, her skin sensitivity decreased to 1 μ g/ml, and she tolerated a cumulative dose of 50.35 μ g of HBV. On the

second day, a cumulative dose of 230 μ g of HBV had been reached without adverse reactions. On the third day, 100 μ g of HBV was given, and after that she received the maintenance dose (100 μ g) at monthly intervals without any problem.

Immune parameters

HBV-induced basophil histamine release. Leukocytes isolated from the patient were challenged with different concentrations of HBV. As shown in Fig. 2, HBV induced basophil histamine release

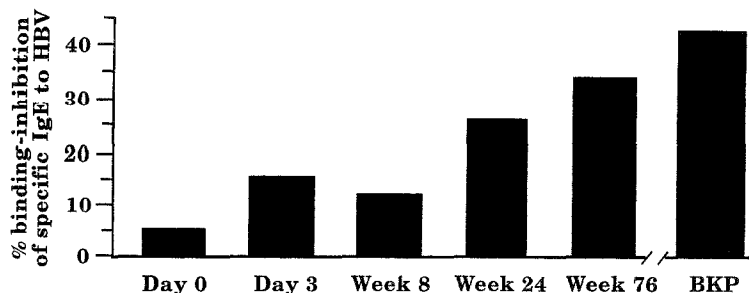


FIG. 3. Determination of ald Abs by binding inhibition of IgE HBV to solid-phase-fixed HBV. All sera and plasma were depleted of anti-HBV activity.

in a dose-dependent fashion. Immediately after infusion of BKP (day 0) and just before initiation of rush immunotherapy (day 3), the antigen-induced basophil histamine release went from 85% to 43% with a concentration of 100 ng/ml of HBV. After 76 weeks of immunotherapy, the percentage of histamine release in our desensitized patient has returned to the level of the nonallergic control subject (i.e., 8% with maximal concentration of antigen). Moreover, the decrease of basophil sensitivity was not associated with a change in the histamine cytoplasmic pool (not shown).

Levels of specific antibody (IgE and IgG). Specific antibody levels to HBV (IgE and IgG) in patient's serum are shown in Table I. Levels of IgE and IgG HBV were comparable before and immediately after infusion of BKP. Levels of IgG HBV were 320 U/ml before initiation of rush antibody. They reached a peak of 1080 U/ml during week 8 and declined slowly in the following months. Levels of IgE HBV remained elevated (upper limit of the sensitivity of the assay) in the first 20 weeks after initiation of antibody. Levels of specific IgE began to decrease in week 24 to reach 2.3 Phadebas RAST units/ml in week 76.

Levels of ald Abs in patient's serum and BKP

Levels of ald Abs were detected with two different methods. First, by binding inhibition of specific IgE antibody to HBV with idiotype-depleted samples, we demonstrated the presence of ald Abs in the serum of the patient and in BKP (Fig. 3). Before the administration of BKP, serum from the patient depleted of idiotype activity had a maximal binding-inhibition activity of 5%. However, the percentage of binding inhibition rose along with immunotherapy to reach a maximum of 33% after 76 weeks of treatment. Significant levels (maximal binding inhibition of 43%) of ald Abs were also found in BKP.

We also evaluated the presence of ald Abs by immunodot technique. Immunoglobulin fractions

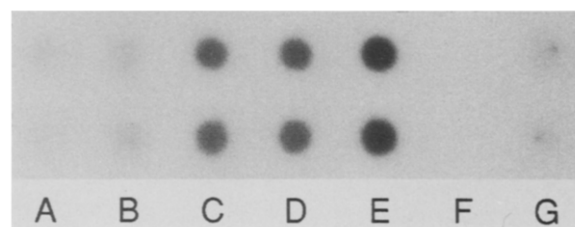


FIG. 4. Determination of ald Abs with immunodot technique. Duplicate of IgG fractions of patient's sera and BKP were dotted onto nitrocellulose sheets and incubated with radiolabeled anti-HBV antibody. In lane A the patient's serum before passive infusion of BKP (day 0) and in lane B the patient's serum after passive transfer but before initiation of rush immunotherapy (day 3) have been dotted onto nitrocellulose sheet. Lanes C and D represent the dotprints of the patient's serum drawn at week 8 and week 24, respectively. In lanes E, F, and G plasma from a nonatopic beekeeper, affinity-purified anti-HBV (10 µg), and serum from a nonatopic subject were dotted onto nitrocellulose sheet.

from patient's serum or BKP were dotted on nitrocellulose sheets and incubated with labeled affinity-purified antibody to HBV. As shown on Fig. 4, the presence of ald Abs was not detectable before passive antibody (lane A). However, ald Abs could be detected 2 days after the infusion of BKP (lane B) and increased during immunotherapy (lanes C and D). High levels of ald Abs could also be measured in BKP (lane E). Serum from normal subjects without known allergies to insect stings also had low levels of ald Abs (lane G). To ensure that affinity-purified anti-HBV used in this assay did not contain Fc-binding rheumatoid factors, this material was dotted onto a nitrocellulose sheet. Incubation with labeled anti-HBV did not reveal the presence of such factors (lane F).

Anti-idiotypic antibodies in BKP recognized a common idiotype in IgE HBV

The binding inhibition of IgE antibody from seven different patients (including the patient

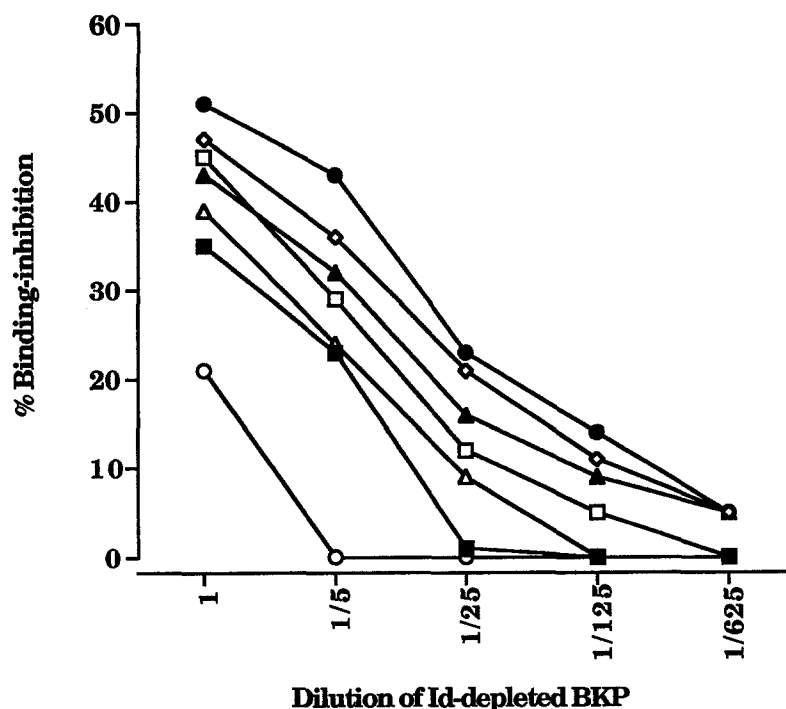


FIG. 5. Binding inhibition of IgE antibody to HBV by BKP depleted of anti-HBV activity. Serum was obtained from seven honeybee sting-sensitive patients (including the patient who received BKP). The data represent the percentage inhibition of IgE binding in the RAST. *Id*, Idiotypic.

who received BKP) to HBV by BKP depleted of idiotype activity is illustrated in Fig. 5. These data suggest that aId Abs contained in BKP recognized idiotypic determinants common in all of these patients. Except in the case of one patient, maximal binding inhibition ranged from 35% to 52%. To ensure that no HBV may have leached off the column when BKP was depleted of anti-HBV activity, a solution of 3% of bovine serum albumin in phosphate buffer was passed through the HBV affinity column before purification of anti-HBV antibody. This solution could not inhibit the binding of IgE antibody from the HBV-sensitive patients to the antigen.

DISCUSSION

Evidence supports a role of aId Abs in the regulation of IgE antibody and suggests that aId Ab levels are associated with successful immunotherapy.^{15, 16, 20} In this report after passive and active immunization, we demonstrated that the increased levels of aId Abs in the serum of a patient highly sensitive to HBV are associated with a diminution of specific antibody (IgG and IgE) to HBV, suggesting an immunoregulatory role of aId Abs. In addition, our data may also demonstrate that aId Abs could be implicated in

the short-term clinical improvement immediately observed after BKP transfusion.

We reported a decrease of the clinical sensitivity to HBV after passive administration of BKP in spite of high levels of specific IgE and no change in the IgG HBV titers. Indeed, during the days after passive administration, the patient tolerated a cumulative dose of 280 µg of HBV without adverse reactions. We also observed decreases in skin mast cell and basophil sensitivity. Recently, Mazer and Gelfand²⁴ reported the clinical efficacy of intravenous Ig therapy in patients with steroid-dependent asthma. After high-dose of intravenous Ig therapy, a rapid improvement in the clinical status, within 24 hours, was also observed in the treatment of many autoimmune diseases,²⁵ and there was some indirect evidence that aId Abs were implicated in the beneficial effects of intravenous Ig therapy.^{26, 27} One may postulate that aId Abs would bind to mast cell-bound IgE HBV and work as blocking agents, either by competing with the antigen or by suppressing mediator release. However, to suggest a potential role of aId Abs in passive transfer of BKP, the idiotype of the treated subject must cross-react with the idiotype found in BKP. Plasma depleted of anti-HBV activity could inhibit the binding of

IgE antibodies from this patient and other HBV-sensitive patients. These results indicate that anti-HBV antibodies from allergic patients and beekeepers could share a cross-reactive idotype. Such a cross-reactivity was also observed by Khan et al.²⁰

After the BKP infusion, a modified rush immunotherapy with HBV was initiated. We observed an increase in the levels of aId Abs along with a decrease of IgE and IgG HBV. These findings suggest a regulatory effect of aId Abs on the synthesis of specific antibodies. In human beings aId Abs have also been demonstrated to down-regulate specific IgE response to tetanus toxoid.²⁸ In addition, the presence of naturally occurring aId Abs has been documented in nonallergic donors, as well as in subjects allergic to ragweed pollen,²⁹ ryegrass pollen,^{15, 16, 30} and house dust mites.³¹ Higher levels of aId Abs were detected in the sera of nonallergic subjects than in the sera of atopic patients before immunotherapy. Also, it has been demonstrated that immunotherapy restores levels of aId Abs in the sera of atopic patients to those observed in the sera of nonallergic subjects.¹⁵ These observations suggest that the increase of aId Ab levels is associated with the remission or clinical improvement observed in patients undergoing desensitization therapy.

On the basis of this study, it appears that aId Abs could play a dual role in a combined protocol of passive and active antibody to HBV. The passive administration of aId Abs in BKP led to an immediate decrease of clinical sensitivity along with a decrease of skin mast cell and basophil sensitivity. In the long term, the appearance of auto-aId Abs correlated with a diminution of specific antibody to HBV, suggesting a more prolonged immunoregulatory role for aId Abs. However, further research on the beneficial effects of aId Abs is needed to define their role in protocol. Studies should include more patients, and an aId Ab-rich preparation should be used instead of BKP. Thus it will be possible to acquire a better understanding of the mechanisms involved between aId Abs and the different phases of the immune response.

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