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Chemokine profiles in blood associated with delayed asthmatic response to allergen challenge

Zdenek Pelikan*

Allergy Research Foundation, Effenseweg 42, 4838 BB Breda, The Netherlands

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KEYWORDS
Allergic bronchial asthma;
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Chemokines in peripheral blood

Summary
Background: Patients with bronchial asthma having been challenged with allergen develop various types of asthmatic response, such as immediate (IAR), late (LAR) or delayed (DYAR) response, due to different immunologic mechanisms. The DYAR, beginning 26–32 h, reaching maximum between 32 and 48 h and resolving within 56 h after the challenge, differs from IAR and LAR in clinical and immunologic features.
Objectives: To investigate the changes in the serum concentrations of chemokines associated with the isolated form of DYAR.
Methods: In 22 patients the repeated DYAR ($p < 0.001$) was supplemented with recording of blood cell counts and serum concentrations of chemokines before, and up to 72 h after the bronchial challenge by means of enzyme-linked immunoassay, (ELISA).
Results: The DYAR was associated with (a) significantly increased serum concentrations ($p < 0.05$) of CCL 2, CCL 3, CCL 4, CCL 7, CCL 20, CXCL 1, CXCL 8, CXCL 9, CXCL 10 and CXCL 11, and (b) significantly decreased serum concentrations, ($p < 0.05$) of CCL 5, CCL 11, CCL 17, CCL 22, CCL 24 and CCL 26, as compared with their pre-challenge as well as the PBS control values. No significant chemokine changes were recorded during the PBS controls ($p > 0.1$).
Conclusions: These results, together with changes in the blood cell counts, provide evidence for an involvement of activated Th_1, cells and NK cells (CCL-2, -3, -4, -20, CXCL-9,-10,-11), neutrophils (CCL-20, CXCL-1,-8) and monocytes (CCL-2,-3,-4, -7, CXCL-10), upon co-operation of other cell types, such as epithelial, endothelial and dendritic cells, in the immunologic mechanism(s) underlying the DYAR.

* Tel.: +31 76 522 30 74; fax: +31 76 520 06 07.
E-mail address: zpelikan@casema.nl.

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Introduction

Various immunologic mechanisms can be involved in various clinical phenotypes of allergic bronchial asthma.[1–6] Besides the already established classic immediate hypersensitivity based upon participation of IgE antibodies, mast cells/basophils, eosinophils and Th_2-lymphocytes, other hypersensitivity mechanisms can also play a role in this condition.[1–15] Patients with bronchial asthma develop various types of asthmatic response to bronchial allergen challenge, such as immediate (IAR),late (LAR) or a dual late (DLAR; a combination of an immediate and a late) asthmatic response. The IAR, LAR and DLAR have already been extensively studied from various points of view.[5,12,16–28]

Some patients with bronchial asthma, examined at our clinic, developed an asthmatic response appearing 26—56 h after the bronchial challenge with various inhalant allergens.[29–32] This response phenotype, designated by us as "delayed asthmatic response" (DYAR), displayed clinical and immunologic features different from those associated with the IAR and the LAR.[2,3,5–12,19,21,25–28]

The key clinical aspect of the DYAR was it onset later than 26 h after the allergen exposure,[29–32] whereas the most important immunologic feature seems the predominant role of activated Th_1 —cells, neutrophils and monocytes in the mechanism(s) underlying the DYAR.[29–32] The DYAR was associated with increased counts of total leukocytes, lymphocytes, neutrophils and shifting of the Th_1/Th_2 ratio in favor of Th_1 cells in peripheral blood,[29–32] increased intracellular concentrations of IFN-γ and IL-2, but not of IL-4 or IL-5, in PBMC,[29] increased serum concentrations of sICAM-1, sVCAM-1, sPECAM-1, sE- and sL-selectins, whereas decreased concentration of sE-cadherin,[30] increased plasma concentrations of LTB_4 and MPO,[31] and increased serum concentrations of some cytokines, such as IFN-γ, IL-2, IL-18, G-CSF, TNF-α and TGF-β.[32]

The purpose of this study was to search for the possible changes in concentrations of other important components of immunologic system, the particular chemokines, in peripheral blood during the DYAR and in this way to contribute not only to assessment of the role of individual cell types in the DYAR, but also to the clarification of the immunologic mechanism(s) underlying this response type.

Methods

Patients

Some of bronchial asthma patients referred to our Department of Allergology &Immunology, Inst. Med. Sci. *De Klokkenberg*, Breda, The Netherlands, for more extensive diagnostic and therapeutic analysis have developed an isolated form of delayed asthmatic response (DYAR), appearing later than 24 h after the bronchial challenge with allergen (BPT, Fig.1). Twenty-two patients developing the DYAR have volunteered to participate in this study (Table 1).

These patients, 19—43 years of age, suffering from reversible bronchial constriction, alternating with symptom-free periods, showed pulmonary function without any restrictive changes (GINA).[33] They did not suffer from current airway infections and did not use oral corticosteroids or receive immunotherapy. They were examined by routine diagnostic procedure, serving also as an exclusion criteria, consisting of a number of diagnostic parameters

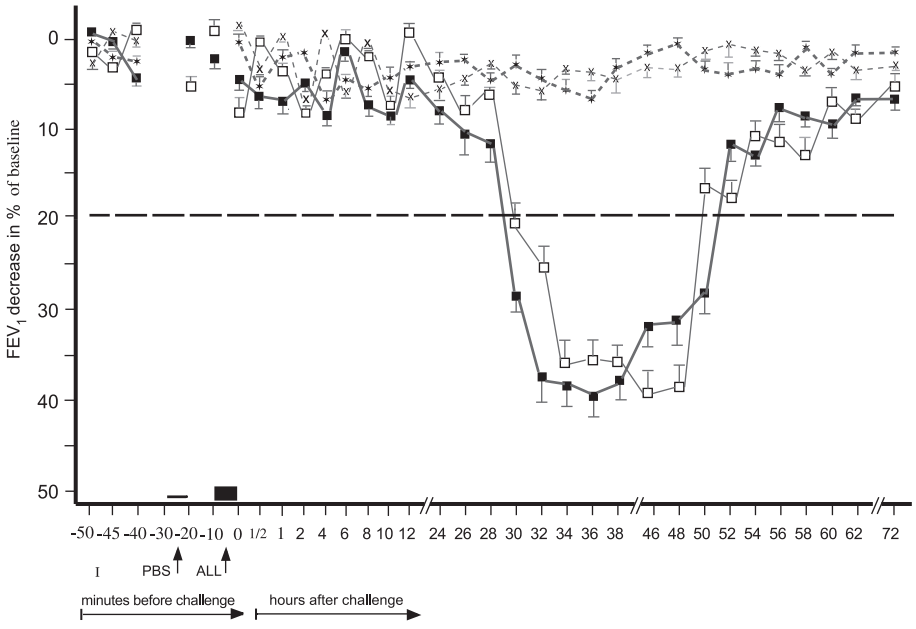

Figure 1 The initial and repeated delayed asthmatic response to allergen challenge (DYAR) and phosphate buffered saline (PBS) control challenge. The mean percentage changes in the FEV_1 values with respect to the baseline values were calculated from 22 DYARs and 22 PBS control challenges; (□) = initial DYAR; (■) = repeated DYAR; (*) = initial PBS; (×) = repeated PBS. I = initial (baseline) values; ALL = allergen challenge; PBS = phosphate buffered saline; Bars = means ± SEM; Dashed horizontal line = statistically significant decrease of FEV_1 values (>20%).