

**Modulation of Cytokine Production by Mononuclear Cells
in Allergic Inflammation.
The Effects of Allergen Exposure and Anti-inflammatory Agents.**

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Göteborgs Universitet kommer att
offentligen försvaras i föreläsningssal Herman Krefting I, Bruna stråket 11B,
Sahlgrenska Universitetssjukhuset

Fredagen den 10 oktober 2003, kl 13.00

av

Katarzyna Wosińska-Becler



Fakultetsopponent: Dr. Christopher J. Corrigan, Guy's, King's and St. Thomas' School of
Medicine, King's College, University of London, UK.

Avhandlingen baseras på följande delarbeten:

- I. **Katarzyna Wosińska-Becler**, Halina Plewako, Lena Håkansson, Sabina Rak. Cytokine production in peripheral blood cells during and outside the pollen season in birch allergic patients and non-allergic controls. (submitted)
- II. **Katarzyna Becler**, Lena Håkansson, Sabina Rak. Treatment of asthmatic patients with a cysteinyl leukotriene receptor 1 antagonist, montelukast (Singulair®) decreases the eosinophil survival enhancing activity produced by peripheral blood mononuclear leukocytes *in vitro*. *Allergy* 2002;57:1021-1028
- III. **Katarzyna Wosińska-Becler**, Monica Arvidsson, Janne Björkander, Per Stahl Skov, Lena Håkansson, Sabina Rak. Basophil IL-4 and IL-13 production is suppressed during the early phase of rush immunotherapy. (manuscript)
- IV. **Katarzyna Wosińska-Becler**, Monica Arvidsson, Janne Björkander, Lena Håkansson, Sabina Rak. Increased IL-12 production by monocytes and IFN- γ by NK cells in allergic patients during rush immunotherapy. (manuscript)

Göteborg 2003

Abstract

**Modulation of Cytokine Production by Mononuclear Cells
in Allergic Inflammation.
The Effects of Allergen Exposure and Anti-inflammatory Agents.**

Katarzyna Wosińska-Becler

Department of Respiratory Medicine and Allergology,
The Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

In pollen-sensitized subjects, seasonal allergen exposure results in clinical allergic disease, which in affected tissues displays a morphological picture typical of chronic inflammation. The cellular responses to allergens include the production of inflammatory cytokines that can be examined in peripheral blood cells. Montelukast (CysLTR₁ antagonist) is a new pharmacological agent used in the treatment of allergic disease with an anti-inflammatory effect that is possibly mediated through reduced cytokine production by mononuclear cells (MNC). Rush immunotherapy (RIT) exerts long-term immunomodulatory effects but the mechanisms of the early tolerance induction in treated patients are unknown. Data concerning functional modulation of cell populations other than T-lymphocytes by RIT are very limited.

The aims of this thesis were (I) to study cytokine production in blood T cells and monocytes obtained from birch-allergic patients during and outside the pollen season; (II) to assess the effect of montelukast treatment on the production of eosinophil survival enhancing cytokines by MNC; (III) to investigate the effects of RIT on activation and cytokine production in blood basophils and (IV) on the expression of costimulatory molecules and cytokine production in MNC.

Following *in vitro* allergen stimulation, monocytes obtained from allergic subjects produced more GM-CSF and less IL-12 compared with healthy controls. In allergic patients, seasonal pollen exposure resulted in increased numbers of GM-CSF⁺ cells among both monocyte and CD4⁺ T cell populations. A seasonal increase in the Th2/Th1 cytokine ratio required an adequate and prolonged allergen stimulation that was seen late in the pollen season.

Treatment of patients with montelukast decreased the production of MNC-derived cytokines i.e. GM-CSF, IL-5 and INF- γ , where GM-CSF was the predominant cytokine responsible for the eosinophil survival-enhancing activity. The *in vitro* results suggested that CysLTR₁ antagonists might act by suppressing GM-CSF production by monocytes. Early in the course of treatment, RIT suppressed basophil number, activation and cytokine production in the blood of treated subjects. Moreover, the ability to produce IL-4 and IL-13 by basophils was related to the extent of the side effects caused by RIT. Immunotherapy also increased the numbers of IL-12⁺ monocytes and IFN- γ ⁺ NK cells in the circulation and decreased the expression of co-stimulatory molecules on blood monocytes (CD86) and CD4⁺ cells (CD28).

In conclusion, the findings of this study emphasize the importance of monocytes as a source of cytokines participating in the development of allergic inflammation. CysLTR₁ antagonists may act by diminishing the production of GM-CSF, possibly from PB monocytes. The ability of basophils to produce IL-4 and IL-13 following allergen stimulation correlated with the side effects of immunotherapy. The number of IL-4 and IL-13 producing basophils and the levels of basophil activation markers and histamine release decreased in the course of the treatment. The restoration of the cytokine imbalance by immunotherapy is not only restricted to the cells of the adaptive immune system but also involves cells comprising the innate immune system.

Key words: cytokines, seasonal allergy, kinetics, CysLTR₁ antagonist, montelukast, rush immunotherapy, monocyte, basophil, eosinophil, NK cell, T cell.

ISBN 91-628-5819-X