Egypt J Pediatr Allergy Immunol 2003; 1(1): 46-53.

Original article

Expression of CD80 and CD86 on T lymphocytes and monocytes of asthmatic children.

Background: *For T lymphocytes to get optimally activated, they need costimulatory signals that can be provided efficiently by costimulatory molecules CD80 and CD86*
Objective: *This study was done to assess the expression of costimulatory molecules CD80 and CD86 on T lymphocytes and monocytes of asthmatic children. The effect of clinical grading of asthma and intake of inhaled steroids on the level of their expression was assessed.*
Methods: *The study included 44 asthmatics (12 with acute asthma and 32 in between attacks) and 12 controls. The asthmatic children were classified according to clinical severity into mild (15 cases), moderate (9 cases) and severe (8 cases). Flow cytometry was performed to analyze the expression of CD80 and CD86 on blood T lymphocytes and monocytes*
Results: *The percentage of expression of costimulatory molecules CD80 and CD86 on T lymphocytes and monocytes were statistically higher in asthmatic children whether in acute or in between attacks compared to the control group ($p<0.05$). This up regulation suggests their critical role in pathogenesis of bronchial allergic inflammation in asthma. The percentage of expression of CD80 and CD86 on monocytes were significantly higher in asthmatics during their acute exacerbations compared to those in between attacks ($p<0.05$). Comparing the clinical subgroups of asthma, there was no statistically significant difference between mild and moderate asthmatics as regards level of co-expression ($p > 0.05$); however the difference was statistically significant between mild and severe cases ($p <0.05$). Asthmatics on inhaled steroids showed significant lower percentage of CD80 and CD86 expression on T lymphocytes and monocytes.*
Conclusion: *The enhanced expression of both CD80 and CD86 on antigen presenting cells and T lymphocytes in bronchial asthma is probably involved in the establishment and maintenance of chronic inflammation of the airways.*

Key words: Asthma, T lymphocytes, Costimulation, CD80 and CD86.

Eman M. Fouda, Shereine Abd El-Fattah, Amal Z. Abd El Halim*.

From the Departments of Pediatrics and Clinical Pathology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.*

Correspondence:
Assist. Prof. Eman Mahmoud Fouda
Pediatric Hospital, Ain Shams University, Abbassiah, Cairo, Egypt.
Fax: 002-02-4852971
e-mail: fouda_eman @ hotmail.com

INTRODUCTION

The concept of costimulation has changed the way of understanding how T cells recognise and respond to antigens [1]. The current model of T cell activation requires two signals:

Signal 1: It is only an initiation event. It requires T cell receptor recognition and binding to antigen presented by antigen presenting cells. However this signal alone is necessary but not sufficient to induce T cell proliferation.

Signal 2: It is a costimulatory signal. It results from binding of one of both molecules of B7 family (CD80 and CD86) on antigen presenting cells to one of two receptors on T lymphocytes (CD28 and cytotoxic T lymphocyte antigen CTLA4).

If both signals are provided, it results in T cell clonal expansion and in the induction of effector functions such as lymphokine production, T cell proliferation and cytokine secretion [2].

Costimulation is required for a productive immune response to occur. The lack of costimulation after engagement of T cell receptor by antigen results in a state of antigen specific unresponsiveness termed anergy. This places the costimulation pathway at a key location for controlling immune response. It also gives it a potential role in treatment of diseases such autoimmune diseases, organ rejection and tumour immunity [2].

The B7 family of costimulatory ligands currently has two members, B7-1 (CD80) and B7-2 (CD86). Both B7-1 and B7-2 belong to the immunoglobulin gene superfamily [3]. CD80 is a 55-kDa glycoprotein made up of 288 amino acids with transmembrane region and a short 19 amino acid cytoplasmic domain[4].

CD86 is a 70-kDa glycoprotein made up of 329 amino acids, a transmembrane region and a longer cytoplasmic domain than CD80 containing potential phosphorylation sites for protein kinase. This indicates that B7-2 may have a signalling function [5].

This study was done to assess the expression of costimulatory molecules CD80 and CD86 on T lymphocytes and monocytes of asthmatic children. The effect of clinical grading of asthma and intake of inhaled steroids on the level of expression of costimulatory molecules was assessed.

METHODS

This study was conducted on 56 children, 41 males and 15 females, during the period from February 2002 to August 2002. They were divided into two groups:

Group I: Asthmatics: This included 44 patients (33 males and 11 females); their ages ranged from 2 to 14 years with a mean age of 6.50±2.65 years. The mean age of onset of asthma was 2.53±1.61 years and the mean duration of illness was4.33± 2.42 years. They were selected from patients attending the Chest Clinic, Children's Hospital, Ain Shams University for follow up.

The asthmatic children were classified into 2 subgroups:

(1) Asthmatics in acute attack:

These included 12 children, 9 males and 3 females, with a mean age of 7.11±3.1 years and a mean duration of illness of 4.6±2.7 years.

(2) Asthmatics in between attacks:

They comprised 32 children (24 male and 8 females) with a mean age of 6.50±2.71 years and a mean duration of illness of 4.09±2.15 years. They were further subdivided into the following clinical subgroups according to the revised GINA guidelines criteria [6]:

Group Ia: Mild persistent asthmatics: 15 children (11 males and 4 females) with a mean age of 5.6±2.0 years and duration of illness of 3.4±2.1 years.

Group Ib: Moderate persistent asthmatics: 9 children (6 males and 3 females) with a mean age of 6.5±1.8 and duration of illness of 4.2±1.5 years.

Group Ic: Severe persistent asthmatics: 8 children (7 males and 1 female) with a mean age of 8.3±3.9 years and duration of illness of 5.2±2.7 years.

According to intake of inhaled steroids, asthmatics were subdivided into:

I) Asthmatics on inhaled steroids: These were 20 children (14 male and 6 females) with a mean age of 7.8±2.9 years and a mean duration of illness of 4.9±2.3 years. They were on fluticasone inhalers (50-125 μg/puff).

II) Asthmatics not receiving inhaled steroids: They comprised 24 children (17 males and 7 females), with a mean age of 5.6±2.1 years and mean duration of illness of 3.5±1.9 years.

Group II: Controls

This group included 12 healthy age and sex-matched children for comparison.

The studied asthmatic children were subjected to:

A. Full history taking, laying stress on duration of disease, frequency of acute attacks, nocturnal symptoms predisposing factors, drug therapy and degree of clinical severity.

B. Clinical examination including examination of the chest.

C. Laboratory investigations including:

1. Complete blood count using Coulter (T-540 cell counter) with peripheral blood film examination stained with Leishman stain especially for lymphocytic and monocytic counts.
2. Estimation of percentage of CD80 and CD86 expression on T lymphocytes and monocytes. The cell surface markers of both CD80 and CD86 were assessed by flow cytometry [7,8] on Coulter Epics XL flow cytometry (Coulter electronics, Hielaeh FI, USA). The surface marker analysis was done on whole blood. The erythrocytes were lysed by adding 3ml NH_4CL (0.83% buffered with $KHCO_3$ pH 7.2) for 5 minutes at 37° C. The CD80 labeled to FITC (Fluorescein Isothiocyanate) and the CD86 labeled to PE (Phycoerythrin) (Cymbus Biotechnology LTD, Units J and K, Eagle close, Chandlers Ford, Hants, S053 4NF, UK). Both parameters were run along with negative isotypic controls (Coulter electronics). A sample was considered positive for CD80 or CD86 when >20% of cells showed the marker.

RESULTS

The results of this study showed that the percentage of CD80 (30.6±18.02) and CD86 (22.11±13.47) expression on T lymphocytes in asthmatics in acute attack were significantly higher than in the control group (CD80 12.25± 5.65, CD86 8.63±5.24, $p<0.05$). On monocytes, the percentage of CD80 (81.78±10.99) and CD86 (87.33±8.05) expression in asthmatics during acute exacerbation were significantly higher than in control group (CD80 45.13±17.02, CD86 50.38± 18.24; $p<0.01$), (Table 1).

In the present study, there was a statistically significant higher percentage of expression of both CD80 and CD86 on monocytes in asthmatics in between attacks compared to control ($p<0.01$), while no statistical significant differences as regards percentage of expression on T lymphocytes ($p>0.05$), (Table 2 and Fig 1).

Comparison between asthmatics in acute exacerbation and those in-between attacks revealed presence of a statistically significant higher percentage

of expression of both CD80 (81.78±10.99) and CD86 (87.33±8.05) on monocytes in acute asthmatic attacks; meanwhile no similar relation could be elicited in the expression on T lymphocytes during acute attacks (30.6±18.02 and 22.11± 13.47 respectively) compared to asthmatics in-between attacks (CD80 20.57±19.94, CD86 12.09±15.98) (p> 0.01) (Fig 2)

The results showed a statistically significant difference between severe asthmatics and both mild and moderate subgroups (p<0.05) as regards coexpression lymphocytes in-between attacks. In addition, there was no statistical significant difference between mild and moderate subgroups as regards levels of coexpression on both lymphocytes and monocytes (Tables 3 and 4).

Concerning the effect of inhaled steroids, the study revealed lower expression of CD80 (15.12±19.04) and CD86 (11.03±13.84) on T lymphocytes in asthmatics on inhaled steroids compared to those who were not (CD80% 26.76± 19.29, CD86% 25.48±17.09; p<0.05). On monocytes, there was significant decrease of expression of CD80 (63.60±20.71) and CD86 (65.8± 28.51) compared to those not receiving steroids (CD80 77.04±19.24, CD86 75.62±26.09) (p< 0.05)(Fig 3).

There was no statistical significant correlation between percentage of coexpression and the clinical parameters of asthmatic children (p> 0.05) (Table 5).

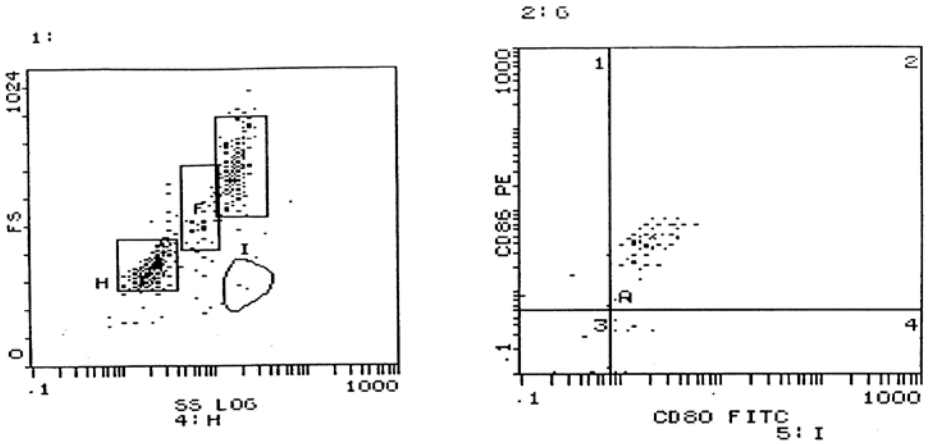

Fig. (1): Example of histogram generated from a case showing expression of CD80 and CD86 on monocytes (coexpression 78.4%).

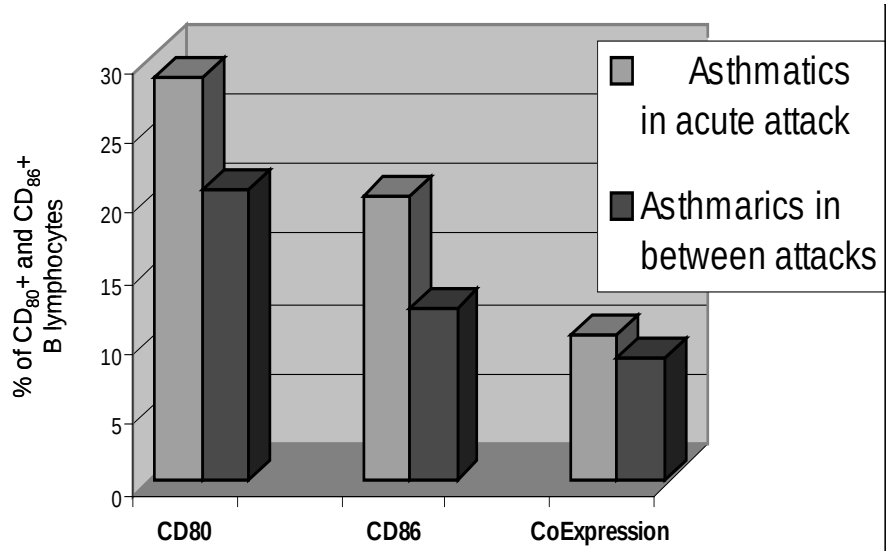

Fig (2): Comparison between asthmatics in acute attacks and asthmatics in-between attacks as regards mean percentage of CD80 and CD86 expression on T lymphocytes.

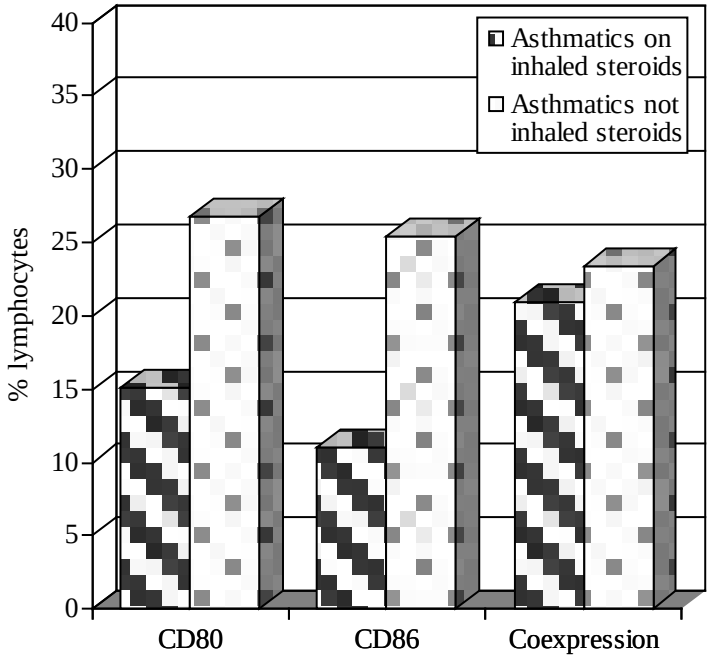

Fig (3): Comparison between asthmatics on inhaled steroids and asthmatics not on inhaled steroids as regards mean percentage expression of CD80 and CD86 on T lymphocytes.

Table (1): Statistical comparison between asthmatics in acute attacks and controls as regards percentage of CD80 and CD86 expression on T lymphocytes and monocytes.

Variable	Asthmatics in acute attack (n=12) Mean ±SD	Controls (n=12) Mean ±SD	t	p
Expression on T Lymphocytes				
CD80 (%)	30.6±18.02	12.25±5.65	2.45	**<0.05 (S)**
CD86 (%)	22.11±13.47	8.63±5.24	2.26	**<0.05 (S)**
Coexpression	14.82±29	5.63±3.16	0.29	>0.05
Expression on Monocytes				
CD80 (%)	81.78±10.99	45.13±17.02	5.34	**<0.001 (HS)**
CD86 (%)	87.33±8.05	50.38±19.50	5	**<0.01 (HS)**
Coexpression	63.55±33.89	37.5±18.24	0.45	>0.05

Table (2): Statistical comparison between asthmatics in-between attacks and controls as regards percentage expression of CD80 and CD86 on T lymphocytes and monocytes.

Variable	Asthmatics between Attacks (n=32) Mean ± SD	Controls (n=12) Mean ± SD	t	p
Expression on T Lymphocytes				
CD80 (%)	20.57±19.94	12.25±5.65	1.15	>0.05
CD86 (%)	12.09±15.98	8.63±5.24	0.6	>0.05
Coexpression	8.63±15.66	5.63±3.16	0.53	>0.05
Expression on Monocytes				
CD80 (%)	69.07±21.82	45.13±17.02	2.068	**<0.01 (HS)**
CD86 (%)	65.87±28.32	50.38±19.50	2.19	**<0.05 (S)**
Coexpression	58.71±26.92	37.5±18.24	2.016	**<0.05 (S)**

Table (3) Statistical comparison between asthmatic subgroups as regards percentage of CD80 and CD86 coexpression on T lymphocytes

	Mild persistent n=15	Moderate persistent n=9	Severe persistent n=8
Mean ±SD	5.59±4.33	3.79±4.33	19.78± 16.11
Vs Mild **t** **p**		0.98 >0.05	1.38 >0.05
Vs Moderate **t** **p**			1.84 < 0.05

Table (4): Statistical comparison between asthmatic subgroups as regards percentage of coexpression of CD80 and CD86 on monocytes.

	Mild persistent n=15	Moderate persistent n=9	Severe persistent n=8
Mean ±SD	66.0±28.48	56.56±26.43	48.13± 23.63
Vs Mild **t** **P**		0.76 >0.05	1.5 >0.05
Vs Moderate **t** **P**			0.67 >0.05

Table (5): Statistical correlation between coexpression of CD80 and CD86 on T lymphocytes and monocytes with some clinical some clinical parameters of the studied groups.

	Coexpression on T lymphocytes		Coexpression on monocytes	
	r	p	r	p
Age of onset (years)	-0.202	>0.05	0.148	>0.05
Asthma duration (years)	0.196	>0.05	0.149	>0.05
IgE (IU)	-0.194	>0.05	-0.327	>0.05
TLC (cells 10^3/mm)	0.186	>0.05	-0.423	>0.05
Absolute lymphocytic count (cells 10^3/mm)	-0.451	>0.05	-0.738	>0.05

DISCUSSION

The basic immunologic event in bronchial asthma is the shift of allergen reactive CD4 T lymphocytes towards a Th2 phenotype with the production of Th2 cytokines. Th2 cells can support allergen specific IgE production and eosinophils recruitment[9]. Optimal T cell activation by antigen presenting cells requires costimluatory signals such as interactions of CD80 and CD86 or both with CD28on T lymphocytes [10].

The results of this study showed that, on T lymphocytes, the percentage of CD80 (30.6±18.02) and CD86 (22.11± 13.47) expression in asthmatics during acute attacks were significantly higher than in the control group (CD80 12.25± 5.65, CD86 8.63±5.24), (p <0.05). On monocytes, percentage of CD80 (81.78±10.99) and CD86 (87.33±8.05) expression in asthmatics in acute exacerbation were significantly higher than in control group (CD80 45.13±17.02, CD86 50.38± 18.24) (p <0.01). This was in agreement with Hofer, et al. 1998 [11] who used flow cytometry to analyze expression of both CD80 and CD86 on T lymphocytes. They found that atopic patients with asthma (exposed to allergen) had significantly higher level of CD80 and CD86 expression than atopic patients not exposed to allergen or control subjects. Burastero et al[12] stated that the outcome of antigen recognition in asthmatic children is dependant -at least in part- on the complex interactions between costimulatory molecules on antigen presenting cells (CD80 and CD86) with their ligands on T cells. They added that costimulation is also involved in determining which effect profile will be acquired by T cells Th1 or Th2 phenotype. Colvita et al[13] and Correno and Collins[14] demonstrated that CD80 or CD86 costimulation appears to be necessary for expression of Th2 cytokines in response to allergen in atopic asthmatic children. Either or both these molecules remain possible targets for intervention in asthma.

In the present study, there was a statistically significant higher percentage of expression of both CD80 and CD86 on monocytes in asthmatics in-between attacks compared to control (p<0.01), while no statistical significant differences as regards percentage of expression on T lymphocytes (p>0.05). This may be due to that in chronic asthmatics in-between attacks, the memory and effector T cells are less dependant on costimulatory signals[15]. Hance[16] compared between antigen-presenting ability of isolated macrophages from healthy and atopic children. He found that the poor antigen presenting ability of cells of healthy children is related to reduced expression and/or function of costimulatory molecules on their surface. This is considered a protective mechanism for inhibition of local T cell activation in healthy lung. Bashian et al[17] concluded that the impaired costimulation of antigen presenting cells in normal healthy tissues can lead to tolerance and decrease T cell activation

Also in the present work, percentage of CD80 and CD86 expression on T lymphocytes were higher in

asthmatics in acute attacks than in asthmatics in-between attacks but did not reach statistical significance. However, on monocytes, CD80 and CD86 in asthmatics in acute exacerbation were significantly higher than those in between attacks. This result is in agreement with Nakada et al[18] who reported that the percentage of expression of CD80 and CD86 on T cells in-between attacks was not altered, while their expression on antigen presenting cells as monocytes was significantly upregulated in atopic and non-atopic asthmatics.

Costimulatory molecules (CD80 and CD86) are expressed in a fashion which depends on type and state of activation of cells. Resting monocytes and B cells consecutively express CD86 while CD80 is induced only upon activation [19]. It is still controversial whether and to what extent CD80 and CD86 provide qualitatively different signals to T lymphocytes, and how they affect progression towards Th1 or Th2. The results have been contradictory, Keane Myers et al[20] reported a dependence on CD86 in establishment of allergic inflammation while Tsuyuki et al[21] concluded that CD80 was primarily involved in their animal model. Nakada et al[18] suggested that CD86 induces the differentiation of Th2 cells where as CD80 induces Th1 differentiation. They noticed that on monocytes, CD86 showed more intense induction, peaking at 6 hours and then gradually declining, which could explain the higher level of CD86 expression on monocytes compared to CD80 expression in asthmatics in this study. This suggests that in early stages of immune reactions, antigen presentation by monocytes may become more important than that by B cells. Nakada et al[22] focused on CD80 and CD86 expression on allergen specific T lymphocytes derived from 10 patients with perennial allergic rhinitis and 10 control , stimulated by house dust mite antigen. CD86 on T cells was upregulated earlier in allergen stimulation, and CD80 on T cells was induced later.

Balbo et al[1] studied the expression of CD80 and CD86 on alveolar macrophages in BAL fluid and in parallel the efficiency of antigen presentation was measured in terms of IL-4 and IL-5 production by allergen stimulated T cells. They found that in asthmatic subjects percent of CD80 but not CD86 on alveolar macrophages were increased at base line and did not change following allergen challenge; CD86, membrane expression was up regulated following allergen challenge indicating that CD86 in vivo is up regulated in the 24 hour following allergen exposure and that this modulation is functionally relevant.

Inhibition studies were performed to evaluate the functional relevance of CD80 or CD86 in relation to effector functions on T cells and whether this response involved both CD80 and CD86 stimulation or whether one accessory molecule predominated over the other. Larche et al[23] studied 8 atopic asthmatic subjects and 7 non-atopic control subjects. BAL T lymphocytes were isolated from asthmatic subjects and cultured with allergen. Allergen-induced proliferation of BAL T cells from asthmatic subjects was inhibited by anti-CD86 antibodies, not anti-CD80 antibodies, reflecting the predominant expression of CD86 by both PBMC and BAL cells. In contrast to the airway tissue, Jaffar et al[24] reported that CD86 appears to be the principal costimulatory molecule required for human PBMC response to allergens. They added that allergen responses in the airway mucosal tissue and PBMC differ in the relative contribution of CD80 and CD86 where both are required by asthmatic airway tissue, whereas CD86 is the principal costimulatory molecule in peripheral blood. It is possible that both CD80 and CD86 are expressed at low levels in the airway tissues so either is insufficient to elicit a costimulatory response. Another explanation provided by Balbo et al[1] is that complex interactions involving multiple cell types, take place in asthmatic tissues, making it difficult to prioritize which specific cellular interaction is important in asthma.

In-between attacks, our results showed a statistically significant difference between severe asthmatics and both mild and moderate subgroups ($p<0.05$) in terms of coexpression on T lymphocytes. There was no statistical significant difference between mild and moderate subgroups as regards level of coexpression on both lymphocytes and monocytes. The relation of costimulatory molecules expression to the severity of asthma was demonstrated by the study of Mark et al[25]. They demonstrated that blockade of either CD80 or CD86 can decrease asthma severity via decreasing airway eosinophilia, IgE and AHR. Several studies failed to show statistical significant difference between mild, moderate and severe clinical asthma, as regards pulmonary functions or cytokine levels in BAL or induced sputum. This may suggest that patients clinically graded to be mild asthmatics could have more advanced stage of bronchial inflammation. This was supported by the absence of significance difference in the level of expression of CD80 and CD86 on monocytes in different clinical grades of asthma in the current study.

Concerning the effect of inhaled steroids, our study revealed a statistically significant lower expression of CD80 and CD86 on T lymphocytes in asthmatics on inhaled steroids compared to those who are not ($p<0.05$). On monocytes, there was a lower significant expression of CD80 and, CD86 compared to those not on steroids ($p< 0.05$). Grindt et al[26] studied the influence of glucocorticoids on the regulation of costimulatory signals. Human monocytes were purified

from peripheral blood of healthy volunteers. Expression of CD80 and CD86 were detected by reverse transcription-polymerase chain reaction and flow cytometry in the absence or presence of glucocorticoids. Glucocorticoids selectively inhibited the expression of CD80 while leaving CD86 unaffected. The effect occurs at concentrations that are reached during therapeutical application of the substances in humans. It is mediated via the cytoplasmic glucocorticoid receptor.

This study concluded that enhanced expression of costimulatory molecules CD80 and CD86 on antigen presenting cells is probably involved in the establishment and maintenance of chronic inflammation of airways. Further studies are recommended to evaluate other costimulatory signals necessary for T cell activation which could quantitatively and qualitatively change the T cell response.

REFERENCES

1. **Balbo P, Silvestri M, Rossi GA, Crimi E, Burastero SE.** Differential role of CD80 and CD86 on alveolar macrophages in the presentation of allergen to T lymphocytes in asthma. Clin Exp Allergy 2001; 31(4): 625-36.
2. **Greenfield E A, Khuong AN, Kuchroo VK.** CD28/B7 Costimulation: a review. Crit Rev Immunol 1998; 18: 389- 418.
3. **Fargeas CA, Truneh A, Reddy M, Hurle M, Seet R, Sekaly RP.** Identification of residues in the V domain of CD80 (B7-1) implicated in functional interaction with CD28 and CTLA4. J Exp Med; 1995; 182: 667-75.
4. **Freeman GJ, Borrelio F, Hodes RJ, Reiser H, Gribben JG, Ng JW, et al.** Murine B7-2, an alternative CTLA4 counter-receptor that costimulates T cell proliferation and interleukin 2 production. J Exp Med; 1993; 178: 2185-92.
5. **Truneh A, Reddy M, Ryan P, Lyn S D, Eichman C, Couez D, et al.** Differential recognition by CD28 of its cognate counter receptors CD80 (B7-1) and CD86 (B7.2): analysis by site directed mutagenesis. Mol Immunol1996; 33: 321-34.
6. **Global Initiative For Asthma (GINA).** Global strategy for asthma management and prevention. NIH publication No.02-3658, 2002. Available on http:// www.ginasthma.com.
7. **Loken MR, Stall AM.** Flow cytometry as an analytical and preparative tool in immunology. J Immunol Methods 1982; 50(3): 1285-312.
8. **Coon J S, Landay AL, Weinstein RS.** Advances in flow cytometry for diagnostic pathology. Lab Invest 1987; 57(5): 453-79.
9. **Durham SR, Till SJ, Corrigan CJ.** T lymphocytes in asthma: Bronchial versus peripheral response. J Allergy Clin Immunol 2000; 106 (5): S221-S6.
10. **Lordan JL, Davies DE, Wilson SJ, Dent G, Corkhill A, Jaffar Z, et al.** The role of CD28-B7 costimulation in allergen-induced cytokine release by bronchial mucosa from patients with moderately severe asthma. J Allergy Clin Immunol 2001; 108(6): 976-81.
11. **Hofer M F, Jirapongsananuruk O, Trumble AE, Donald YM.** Upregulation of B7.2, but not B7.1, on B cells from patients with allergic asthma. J Allergy Clin Immunol 1998; 101: 96-102.
12. **Burastero SE, Magnani Z, Confetti C, Abbruzzese L, Oddera S, Balbo P, et al.** Increased expression of the CD80 accessory molecule by alveolar macrophages in asthmatic subjects and its functional involvement in allergen presentation to autologous TH2 lymphocytes. J Allergy Clin Immunol 1999; 103:1136-42.
13. **Colavita AM, Reinach AJ, Peters SP.** Contributing factors to the pathophysiology of asthma. The Th1/Th2 paradigm. Clin Chest Med 2000; 21(2): 263-77, viii. Review.
14. **Correno BM, Collins M.** B7 family of ligands and its receptors:new pathways for costimulation and inhibition of immunresponses. Annu Rev Immunol 2002; 20: 29-53.
15. **Croftd M, Bradely LM, Swain SL.** Naïve versus memory CD4 T lymphocytes response to antigen. J Immunol 1994; 152: 2675.
16. **Hance AJ.** Accessory cell-lymphocyte interactions. In: Crystal RG, Weibel ER, Barnes PJ, editors. The lung: scientific foundations, 2nd ed. Philadelphia: Lippincott-Raven; 1997. p. 821-39.
17. **Bashian GG, Braun CM, Huang SK.** Differential regulation of human, antigen-specific Th1 and Th2 responses by the B-7 homologues, CD80 and CD86. Am J Respir Cell Mol Biol 1997; 17: 235-42.
18. **Nakada M, Nishizaki K, Yoshino T, Okano M, Masuda Y, Ohta N, et al.** 86 (B7-2) antigen on B cells from atopic patients shows selective, antigen-specific upregulation. Eur J Allergy Clin Immunol 1998; 53: 527-31.
19. **Burastero SE, Rossi GA.** Immunomodulation by interference with co-stimulatory molecules: therapeutic perspectives in asthma. Thorax 1999; 54: 554-7.
20. **Keane-Myers A, Gause WC, Linsley PS.** B7-CD28/CTLA-4 costimulatory pathways are required for the development of T helper cell 2-mediated allergic airway responses to inhaled antigens. J Immunol 1997; 158: 2042-9.
21. **Tsuyuki K, Tsuyki J, Einsle K, Kopf M, Coyle AJ.** Costimulation through B7-2 (CD86) is required for the induction of a lung mucosal T helper cell 2 (TH2) immune response and altered airway responsiveness. J Exp Med 1997; 185 (9): 1671-9.
22. **Nakada M, Nishizaki K, Yoshino T, Okano M, Yamamato T, Masuda Y.** CD80 (B7-1) and CD86 (B7-2) antigens on house dust mite specific T cells in atopic disease function through T-T cell interactions. J Allergy Clin Immunol 1999; 104: 222-7.

23. **Larché M, Till SJ, Haselden BM, North J, Barkans J, Corrigan CJ.** Costimulation through CD86 is involved in airway antigen-presenting cell and T cell responses to allergen in atopic asthmatics. J Immunol 1998; 161: 6375-82.

24. **Jaffar ZH, Stanciu L, Pandit A, Lordan J, Holgate ST, Roberts K.** Essential role for both CD80 and CD86 costimulation, but not CD40 interactions, in allergen-induced Th2 cytokine production from asthmatic bronchial tissue: role for αβ, but not γδ, T cells. J Immunol 1999; 163: 6283-91.

25. **Mark D A, Donovan CE, De Sanctis GT.** Both CD80 and CD86. Costimulatory molecules regulate allergic pulmonary inflammation. Int. Immunol 1998; 10: 1647-55.

26. **Girndt M, Sester U, Kaul H, Hunger F, Kohler H.** Glucocorticoids inhibit activation-dependent expression of costimulatory molecule B7-1 in human monocytes. Transplantation 1998; 15; 66(3): 370-5.