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Suplatast Tosilate for Prophylaxis of Pediatric Atopy

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1. Introduction

The onset of asthma may be related to Th2 cytokine dominance at the time when food allergies occur several months after birth. This study investigated the effectiveness of early intervention with a Th2 cytokine inhibitor (suplatast tosilate) for prevention of asthma in infants with food allergies and atopic dermatitis. Suplatast tosilate dry syrup (6 mg/kg daily) or a histamine H1-blocker (ketotifen fumarate dry syrup: 0.06 mg/kg daily) was administered randomly to 53 infants with atopic dermatitis caused by food allergies. The primary endpoints were the incidence of asthma and the time to the onset of wheezing. The peripheral blood Th1/Th2 ratio, total IgE level, and eosinophil count were measured before and after treatment. After 24 months of treatment, the prevalence of asthma was significantly lower in the suplatast group (20.8%) than in the ketotifen group (65.6%, $p < 0.01$). Additionally, the time from the start of treatment to the initial episode of wheezing for infants who developed asthma was significantly longer in the suplatast group than the ketotifen group ($p < 0.01$). Furthermore, the eosinophil count was significantly decreased by suplatast treatment ($p < 0.05$), and there was a significant difference between the suplatast and ketotifen groups with respect to both the eosinophil count ($p < 0.01$) and the Th1/Th2 ratio ($p < 0.05$). The results of the present pilot study suggest that suplatast tosilate is useful for the primary prevention of wheezing and asthma in children.

2. Atopic dermatitis is associated with asthma

Asthma frequently develops by the age of 3 yr (1) and recent research has demonstrated that its onset is tending to occur at a younger age (2). Various hypotheses have been suggested with respect to the etiology of asthma. According to the Tucson cohort study performed in the United States, there is a low probability of atopic asthma developing in infants with recurrent wheezing up to the age of 3 yr, and they are considered to be a separate population from the infants in whom recurrent wheezing persists until later childhood (3). In the former group, viral infection is the direct cause of wheezing, while the latter group have an atopic constitution and their asthma may persist during the school years and even into adulthood. Thus, this latter group may be a population for which early intervention is important. It is known that chronic asthma is more likely to develop in patients who are positive in tests for food or house dust allergens (4, 5). The rate of progression to adult asthma is also high among individuals who test positive for food allergens, such as those in

eggs or milk, during early infancy (6), while another study has shown that the strongest risk factor for life- threatening asthma is the presence of food allergy (7). Atopic dermatitis was reported to be associated with asthma that has a later onset (8), while inhibition of the occurrence of asthma has been reported in dermatitis patients treated with H1-blocker therapy (9, 10).

2.1 Th2 cytokine inhibitor: Suplatast tosilate

We have tested the preventive effect of treatment with a Th2 inhibitor, suplatast tosilate. In previous in vitro and in vivo studies, suplatast tosilate has been shown to inhibit the production of IgE antibodies, reduce tissue eosinophil infiltration, and block the production of IL-4 and IL-5 (11–13). More recently, it was shown to prevent goblet cell hyperplasia by blocking IL-13 production (14). According to a study performed in a mouse model of food allergy, suplatast tosilate decreases IL-4 and IL-6 production in the small intestine, and also ameliorates small bowel necrosis (15). In adults with asthma, suplatast tosilate shows comparable anti-inflammatory activity to inhaled steroids (16), as well as improving lung function, asthma symptoms, and airway hyperresponsiveness (16, 17). In patients receiving high-dose inhaled steroids, addition of suplatast tosilate allows the steroid dose to be reduced (18). Furthermore, evaluation by bronchial biopsy has shown that this drug decreases the number of eosinophils and EG2-positive cells in the airway mucosa, as well as inhibiting goblet cell hyperplasia (17, 19). Infants with a family history of atopy and infants in whom atopic disease occurs soon after birth have been reported to show a shift of the Th1-Th2 cytokine balance towards Th2 dominance (20, 21). Accordingly, the Th1-Th2 balance during the early postnatal period is believed to be a key factor in determining whether or not allergy develops.

2.2 Aim and method of this study

The present study was designed to investigate early intervention in atopic dermatitis patients with food allergies, a population considered to be at high risk for the development of asthma. Suplatast tosilate was chosen for early intervention therapy in the present study based on the hypothesis that selective inhibition of Th2 cytokines would improve the Th1-Th2 balance in the high-risk group for asthma (children with Th2 cytokine dominance). Comparison was made with a histamine H1-blocker, ketotifen fumarate, as the control drug.

2.2.1 Subject

We studied 60 consecutive infants who presented to our department with symptoms of atopic dermatitis caused by food allergies that had persisted for at least 2 month. All of the infants had a family history (at least one parent) of atopic disease, such as bronchial asthma, allergic rhinitis, or atopic dermatitis. The diagnosis of atopic dermatitis was based on the criteria of the Japanese Dermatological Association (22), and all of the infants had predisposing factors for atopic disease (a family history of atopy, a history of allergic disease, or a predisposition to IgE production). They primarily developed pruritic eczema that showed repeated episodes of exacerbation and remission. Only infants with chronic dermatitis that had persisted for 2 months or more were diagnosed as having atopic dermatitis. Food allergies were diagnosed from the history using the following criteria: (i) a history of skin disease influenced by food, and (ii) a raised serum level of specific IgE for cow's milk or egg white (CAP RAST class ‡2). Children were excluded who had a history

suggesting the prior existence of asthma, such as wheeze and chronic cough unrelated to respiratory tract infection. Infants who had used oral sodium cromoglycate or other antiallergy drugs within the previous 4 wk (agents that could potentially affect the outcome of this study) were also excluded, but those using topical steroids rated as medium strength or weak to control atopic dermatitis were permitted to enter the study.

2.2.2 Study design

Thirty children were randomly assigned to oral treatment with suplatast tosilate dry syrup (IPD dry syrup 5%, Taiho Pharmaceutical Co. Ltd, Tokyo Japan) at a dose of 3 mg/kg twice daily (the total daily dose was 6 mg/kg) and 30 were assigned to receive ketotifen fumarate dry syrup at dose of 0.03 mg/kg twice daily (the total daily dose was 0.06 mg/kg). Both these drugs were administered for at least 2 yr, and could be continued for up to 4 yr at the request of the parents. After the start of the study, subjects were reviewed at the outpatient department once monthly until completion of the study. Blood was collected at the start and after 6 months of treatment for measurement of the total IgE level; the specific IgE levels for egg white, cow's milk, Der P, and house dust mite; the eosinophil count; and the Th1/Th2 ratio. The primary endpoints of this study were the incidence of asthma and the time to the initial episode of wheezing among the patients in whom asthma occurred. Wheezing was confirmed by the authors via auscultation, and the date of the initial of wheezing, as well as subsequent episodes of wheezing and persistent cough excluding those caused by infection, was recorded in each infant. Asthma was defined as the occurrence of three or more episodes of wheezing associated with expiratory dyspnea, and the day of onset of asthma was defined as the day when the initial episode of wheezing occurred in each patient with asthma. The secondary endpoints of this study were the percentage of patients admitted to hospital because of asthma and changes of the peripheral blood eosinophil count, IgE level, and Th1/Th2 ratio. For the treatment of atopic dermatitis and food allergies, the use of concomitant drugs other than medium-strength to weak topical steroids was not allowed during the study period. After the onset of asthma, antiasthma medications, mainly anti-inflammatory drugs, could be prescribed.

2.2.3 Measurement of the Th1/Th2 ratio

The Th1/Th2 ratio was measured by flow cytometry using a FACScan (23). In brief, CD4-positive cells (helper T cells) were isolated. Then Th2 cytokine-positive cells were detected and counted after staining with an anti-IL-4 antibody, while Th1 cytokine – positive cells were identified with an anti-IFN-c antibody, after which the Th1/Th2 ratio was calculated.

2.2.4 Measurement of serum total IgE and specific IgE

Serum total IgE was measured using a fluoroenzyme immunoassay (FEIA) (CAP RIST FEIA, Pharmacia, Uppsala, Sweden). The levels of specific IgE for house dust mite, Der P, egg white, and cow's milk were measured using FEIA (CAP RAST FEIA, Pharmacia).

2.2.5 Ethics

This study was approved by the Regional Ethics Committee for Human Research at Dokkyo University School of Medicine Hospital. The parents of all patients participating in this study gave oral and written informed consent.

2.2.6 Statistical analysis

The initial wheezing episodes were plotted by the Kaplan–Meier method, and p-values were calculated with the log-rank test. Pearson's chisquared test was used to analyze the incidence of asthma. The Th1/Th2 ratio, total IgE level, and eosinophil count were compared between before and after treatment using the paired t-test. It was employed to determine the significance of differences between the two treatments. Results were expressed as the mean ± s.e., and p-values of <0.05 were considered to indicate statistical significance.

2.3 Result of this study

A total of seven infants were excluded from the study: three infants were excluded because their parents did not allow their children to receive suplatast tosilate, while four infants were excluded because they stopped attending the hospital for various reasons. As a result, there were 29 infants in the ketotifen group and 24 in the suplatast group. The clinical profile of each group is shown in the Table 1.

	Ketotifen group (n = 29)	Suplatast group (n = 24)	p-value
Sex	Males 22, female 7	Males 18, female 6	0.942
Age (days)	370.9±78.7	365.5±80.5	0.728
Age at onset (days)	145.1±34.5	134.4±19.7	0.633
No. of days from onset to drug treatment (days)	225.8±69.4	231.0±77.7	0.837
Total IgE (IU/ml)	509.2±209.6	745.7±207.0	0.24
Egg IgE (Class)	2.50±0.26	3.36±0.31	0.0188
Milk IgE (Class)	2.09±1.87	3.69±0.37	0.0273
House dust mite IgE (Class)	1.25±0.49	1.56±0.59	0.814
Der P IgE (Class)	1.31±0.48	1.73±0.64	0.752

Table 1. Clinical profile

There were no significant differences between the two groups with respect to the sex ratio, age, time of onset of atopic dermatitis, number of days from onset to drug treatment. The mean age at the start of treatment was 365.5 ± 80.5 days in the 24 infants who received suplatast tosilate and 370.9 ± 78.7 days in the 29 who received ketotifen fumarate.

There were no differences between the suplatast group and the ketotifen group with respect to the total IgE level or the levels of specific IgE for house dust mite or Der P before treatment. However, the specific IgE levels for egg white and milk were significantly higher in the suplatast group.

The incidence of asthma was significantly lower in the suplatast group than the ketotifen group, with asthma occurring in five out of 24 patients from the former group (20.8%) vs. 19 out of 29 patients from the latter group (65.6%, $p < 0.01$). Additionally, the time from the start of drug treatment to the onset of wheezing among patients in whom asthma occurred was significantly longer in the suplatast group than the ketotifen group ($p < 0.01$, Fig. 1). The percentage of infants who were admitted to hospital for the treatment of asthma was significantly lower ($p < 0.05$) in the suplatast group (one out of 24 patients, or 4.2%) than in the ketotifen group (seven out of 29 patients, or 24.1%).

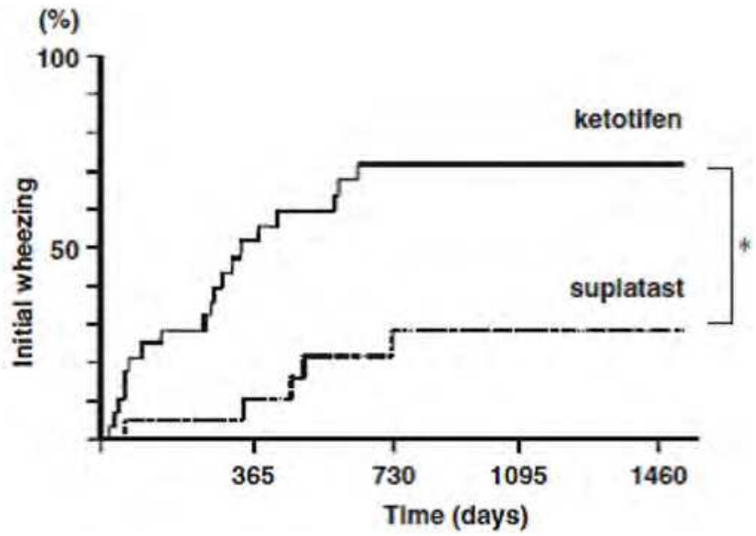

Fig. 1. Onset of wheezing during treatment with a Th2 cytokine inhibitor (suplatast tosilate) or a histamine H1-blocker (ketotifen fumarate).

The eosinophil count decreased significantly from 1.212 ± 174 to 679 ± 111/lL ($p < 0.05$) after 219 ± 42 days of suplatast treatment (n = 21), while no significant change was observed after 280 ± 44 days of ketotifen treatment (n = 19). The change after treatment was significantly larger ($p < 0.01$) in the suplatast group (-532.4 ± 120.0) compared with the ketotifen group (-2.1 ± 126.0) (Fig. 2). Although there was no significant change of the Th1/Th2 ratio after treatment in either the suplatast group (from 4.88 ± 1.07 to 6.76 ± 1.58%, n = 16) or the ketotifen group (from 10.00 ± 8.52 to 6.44 ± 1.88% n = 10), there was a significant difference of the ratio between the two groups ($p < 0.05$) (Fig. 3). However, there was no significant difference between the groups with respect to changes of the total IgE level (data not shown).

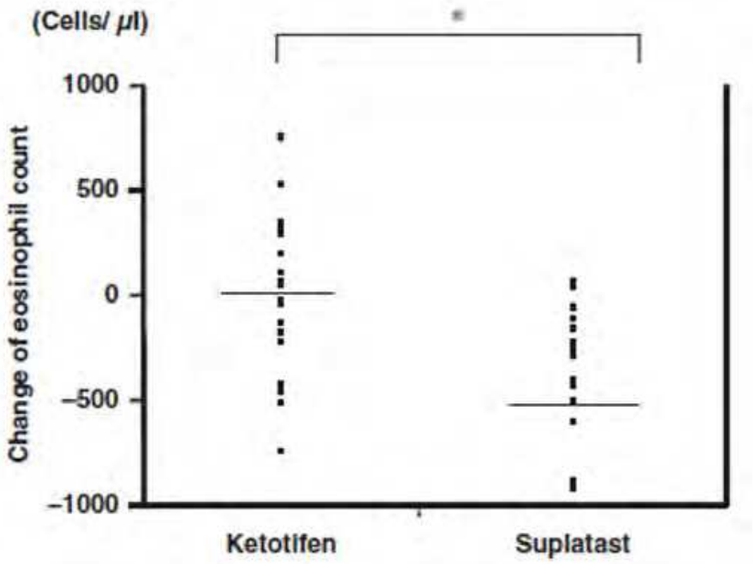

Fig. 2. Eosinophil count before and after treatment with suplatast tosilate (-532.4 ± 120.0) or ketotifen fumarate (-2.1 ± 126.0); *$p < 0.01$ by the t-test.

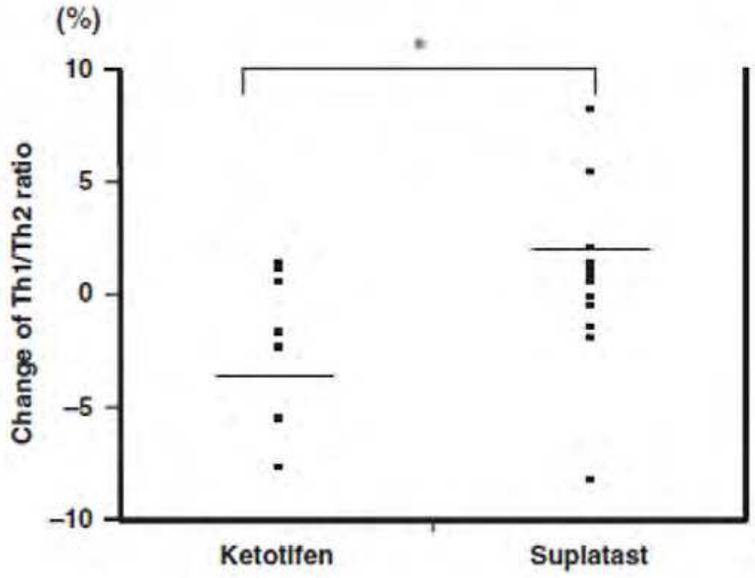

Fig. 3. Th1/Th2 ratio before and after treatment with suplatast tosilate (1.88 ± 1.57) or ketotifen fumarate (-3.56 ± 1.99); *p < 0.05 by the t-test.

No adverse events and no laboratory abnormalities were observed in the suplatast group. Two episodes of sedation occurred in the ketotifen group, but these were transient and did not result in the discontinuation of therapy.

2.4 Effectiveness of early intervention with a Th2 cytokine inhibitor

Children with a family history of allergic disease are likely to have a predisposition to atopy and the processes leading to the development of such diseases may commence in utero. After birth, continuous exposure to certain food antigens may sequentially trigger allergic reactions that manifest as food allergies, atopic dermatitis, asthma, and allergic rhinitis. Such reactions are involved in the progression of allergic disease (24, 25). Treatment designed to suppress the exacerbation of allergic airway inflammation may potentially have an important role in the prophylaxis and management of these diseases.

We compared the inhibitory effect of suplatast tosilate and the H1-blocker ketotifen fumarate on the onset of asthma in patients with atopic dermatitis who were positive for egg-white or milk allergens. When ketotifen was previously tested in 121 infants with atopic dermatitis who were treated for a 1-yr period, it reduced the occurrence of asthma compared with placebo, and the subgroup of children with a high IgE level showed a significant benefit (9). After 24 months of treatment in the present study, however, asthma developed in 65.6% of the patients receiving ketotifen vs. only 20.8% of those treated with suplatast. To assess the prevention of progression to severe asthma, we analyzed the number of patients who required hospital treatment for their asthma. Seven out of 29 infants from the ketotifen group and only one out of 24 infants from the suplatast group were admitted to hospital for the treatment of asthma, with the percentage being significantly lower in the suplatast group. This finding suggests the possibility that suplatast can prevent progression of mild asthma to severe asthma.

To examine the systemic effects of suplatast (a Th2 cytokine inhibitor) vs. those of ketorifen (an antihistamine), the Th1/Th2 ratio, total IgE level, and eosinophil count were measured before and after treatment. As a result, the Th1/Th2 ratio was found to be significantly higher after

treatment in the suplatast group than in the ketotifen group, but neither drug decreased the serum IgE level. Based on the previous report that 3 or 6 months of treatment with suplatast tosilate decreased the serum levels of IgE and IL-4 in adults with perennial allergic rhinitis (26), we assessed the changes of parameters over a 6-month period in this study. The failure of suplatast tosilate to suppress IgE production may have been related to the low age of the subjects in the suplatast group (mean age at the start of treatment with suplatast: 365.5 days), because there is a gradual increase of tolerance to food allergens such as egg white and cow's milk, while sensitization to inhaled allergens like Der P and house dust mite shows a rapid increase at this age and infants with an atopic tendency show increased IgE synthesis at this age (27). Accordingly, we were not able to assess the efficacy of suplatast from the total IgE level. The Early Treatment of the Atopic Child (ETAC) study investigated the use of cetirizine, an H1-blocker like ketotifen for preventing the onset of asthma and found no significant overall benefit compared with the placebo, although asthma was prevented in patients sensitized to house dust mite or grass pollen (10). Our patients had high antibody titers for food allergens, but their mean baseline CAP RAST scores were 2 or less for both house dust mite and Der P. This suggests that suplatast was more effective than H1-blockers for patients who were not strongly sensitized to inhaled allergens. As we did not initially plan to assess changes of specific IgE levels in the present study, these parameters were only measured in a few patients after the start of treatment. Therefore, drawing firm conclusions is impossible, but we plan to investigate further whether suplatast has a similar effect to that of immunotherapy, which prevents the development of new allergies (e.g., suppresses reactions to inhaled allergens) (28). In the present study, we directed our attention to the Th1/Th2 ratio. At birth, the production of INF-c is very low and infants are in a state where the immune response is Th2 dominant. If IFN-c production increases during the 6 months after birth, the immune response will become Th1 dominant and the production of IL-4 will be inhibited, preventing the acquisition of an atopic predisposition. In an environment that does not cause induction of IFN-c, however, its level gradually increases with maturity, but IL-4 also continues to be produced until an atopic predisposition is acquired (29). Our preliminary study showed that persons with a strong atopic predisposition, who developed food allergies followed by atopic dermatitis, asthma, and allergic rhinitis, actually had a higher Th1/Th2 ratio than healthy subjects and had a Th1-Th2 balance skewed toward Th2 dominance (unpublished observation). Such findings suggest that there is a tendency for Th2 dominance in infancy and that an increase of inflammation due to eosinophils, etc. may lead to the eventual onset of asthma. Suplatast has been shown to inhibit the activity of eosinophils by in vitro and in vivo studies, including research performed using peripheral blood, sputum, and bronchial tissue specimens obtained by biopsy (12–14, 16, 17). In the present study, suplatast significantly decreased the peripheral blood eosinophil count compared with ketotifen. There have been several reports of a relationship between the onset of asthma and eosinophils. For example, Bromchoalveolar lavage fluid (BALF) levels of Eosimophilic Catiomic Protein (ECP) are higher in patients with childhood asthma than in those with infantile wheeze (30), and persons who subsequently develop asthma have more Eosimophil Granulocyte-2 (EG2)- positive cells in the epithelium or lamina propria on bronchial biopsy than those who do not (31).

It appears that inhibition of the onset of asthma may be attributable to two factors, which are a decrease of the eosinophil count and a shift of the Th1/Th2 ratio toward Th1 dominance. The results of our study provide some corroboration for the hypothesis that inhibition of eosinophilic inflammation and improvement of the Th1/Th2 balance can contribute to preventing the onset of asthma.

The present investigation was only a pilot study, but it is still clinically significant that more than half of our patients with atopic dermatitis and food allergies developed asthma before age three during treatment with ketotifen, while only 20% of the suplatast group did so. Among the criteria in the asthma predictive index (API) (32), which is based on the Tucson Children's Respiratory Study, as well as the major and minor criteria in the modified asthma predictive index (mAPI) (33) based on the PEAK trial, a parental history of asthma, physician-diagnosed atopic dermatitis, and allergic sensitization to milk, egg, or peanuts correspond to the criteria used in the present study. These other studies have suggested that early intervention with suplatast can prevent progression to chronic asthma if patients meeting the criteria that suggest an increased likelihood of progression to chronic asthma in the future are treated before they develop wheezing. Both the API and the mAPI include the criterion of an eosinophil count ‡4%. Most of the patients in the present study met this criterion and showed a significant decrease of eosinophils after treatment with suplatast. Therefore, early intervention with suplatast may prevent progression to chronic asthma even in patients with a high eosinophil count, who have an increased risk of developing chronic asthma. The finding that a lower percentage of patients in the suplatast group needed hospital admission for asthma also serves as evidence that this drug may prevent progression to chronic asthma.

3. Conclusion

There have only been a few reports about early intervention for patients with a high risk of developing asthma. Iikura et al. reported a research of early intervention (34). To evaluate the prophylactic effect of ketotifen against the onset of asthma they selected 121 infants with atopic dermatitis. A placebo syrup group and an active syrup group were followed for 1 year, with bimonthly evaluations. During the 1 year study, asthma was observed in eight children of the ketotifen group (13.1%) and in 25 children of the placebo group (41.6%) (P less than .001). As a result, they concluded that Ketotifen is effective for early intervention in children with atopic dermatitis.

Suplatast tosilate is an oral agent that has been available in Japan for 12 yr since 1995. It is highly safe, and there have been no reports of serious adverse reactions to this drug (35). The manufacturer of Suplatast, (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) summarized the adverse events that were detected among 154 children under 3 yr old in a study of actual use. According to this report, adverse reactions were only noted in two patients. This shows that Suplatast is also safe for patients under 3 yr old and thus is thus suitable for long-term administration to high risk patients in order to prevent the onset of asthma. It is one of the few drugs available that act as a non-specific regulator of the immune system. Then, it showed that the allergic predisposition is improved in suppressing the symptom. Therefore it can be said that suplatast tosilate is an antiallergic fundamentally curative drug. In the future, we hope to collect more cases and explore whether this drug can change the natural history of asthma.

4. References

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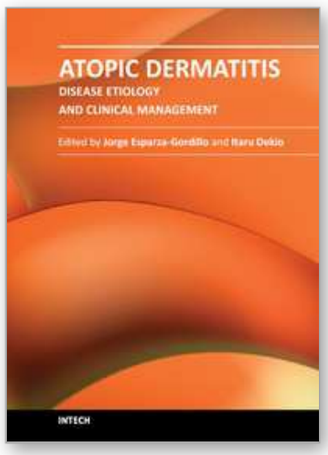

Atopic Dermatitis - Disease Etiology and Clinical Management
Edited by Dr. Jorge Esparza-Gordillo

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Atopic Dermatitis is a common disease characterized by inflamed, itching and dry skin. This relapsing allergic disorder has complex etiology and shows a remarkably high clinical heterogeneity which complicates the diagnosis and clinical management. This book is divided into 4 sections. The first section (Disease Etiology) describes some of the physiological mechanisms underlying Atopic Dermatitis, including alterations in the immune system and the skin-barrier function. The important role of host-microorganism interactions on the pathophysiology of Atopic Dermatitis is discussed in the second section (Microorganisms in Atopic Dermatitis). An overview of the clinical diagnostic criteria and the disease management protocols commonly used is given in the third section (Diagnosis and Clinical Management). The last section (New Treatments) describes new therapeutic approaches that are not widely used but are currently being studied due to preliminary evidence showing a clinical benefit for Atopic Dermatitis.

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