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Short Communication

Keishibukuryogan (Gui-Zhi-Fu-Ling-Wan), a Kampo formula decreases the disease activity and the level of serum thymus and activation-regulated chemokine (TARC) in patients with atopic dermatitis

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Atopic dermatitis (AD) is a chronic inflammatory skin disorder with pruritic and eczematous lesions. AD is characterized by the predominant infiltration of Th2-type cells in the acute phase of skin lesions. Thymus and activation-regulated chemokine (TARC), a member of the CC chemokine superfamily was identified as a selective chemoattractant for Th2-type cells. The serum TARC level is significantly increased in patients with AD and is correlated with the severity of AD. Keishibukuryogan (KBG) is a Kampo formula composed of five kind of crude drugs and has been administered to patients with blood stagnation in Japan. This study investigated the effect of KBG on disease activity and TARC production in AD patients. AD patients were administered KBG for 4 to 6 weeks in addition to their prescribed medications. The SCORAD index and VAS score were decreased by the administration of KBG. The serum TARC level of the AD patients was much higher than that of normal controls. This elevated serum TARC level was significantly decreased by administration of KBG. These results suggest that KBG may improve AD by the inhibitory effect on Th2-type chemokine production.

Key words Atopic dermatitis, Thymus and activation-regulated chemokine (TARC), Keishibukuryogan.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with pruritic and eczematous lesions and is associated with elevated serum IgE levels, specific IgE environmental allergens such as house dust mites, and tissue and peripheral blood eosinophilia. AD is characterized by the predominant infiltration of Th2-type cells, the increased secretion of the Th2-related cytokines, interleukin (IL)-4 and IL-5 in the acute phase of skin lesions.[1] Thymus and activation-regulated chemokine (TARC/CCL17) was a member of the CC chemokine superfamily, produced by monocyte-derived dendritic cells (DCs), endothelial cells and keratinocytes. TARC was identified as a selective chemoattractant for cells expressing CC chemokine receptor4 (CCR4), such as Th2-type cells.[2] The serum TARC level is significantly increased in patients with AD and is correlated with the severity of AD.[3]

Keishibukuryogan (KBG) is a Kampo formula composed of five kind of crude drugs, Cinnamomicorte, Moutan cortex, Paeoniae radix, Persicae semen and Hoelen. KBG has been administered to patients with blood stagnation, such as thrombotic disease and atherosclerosis in Japan. This study investigated the effect of KBG on disease activity and TARC production in AD patients.

Materials and Methods

Patients. The study groups included 36 patients with AD (18 males and 12 females). The mean age was 27.8 ± 6.1 years old. AD was diagnosed according to the criteria of Hannifin & Rajka.[4]

Design of study. These AD patients were administered 2.5 g of KBG (TJ-25; obtained from Tsumura and Co., Tokyo, Japan) three times daily for 4 to 6 weeks in addition to their prescribed medications, such as topical steroid and oral anti-allergic drugs. During the study, other medications could not be newly introduced. Clinical and laboratory assessments were performed at week 0 and week 4 or 6. The study design was approved by the Human Subjects Committee, University of Toyama. All patients provided written informed consent in accordance with the ethical guidelines set forth in the 1975 Declaration of Helsinki.

Clinical and laboratory assessments. The clinical severity of AD was assessed using the SCORing Atopic Dermatitis (SCORAD) index (range 0-103).[5] For the assessment of itch, a visual analogue scale (VAS) score (range 0-100) was used. The serum level of TARC was measured with enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol (R & D System, Minneapolis, USA).

Statistical Analysis. All data were presented as the mean ± S.E.M. The statistical analysis was performed using the

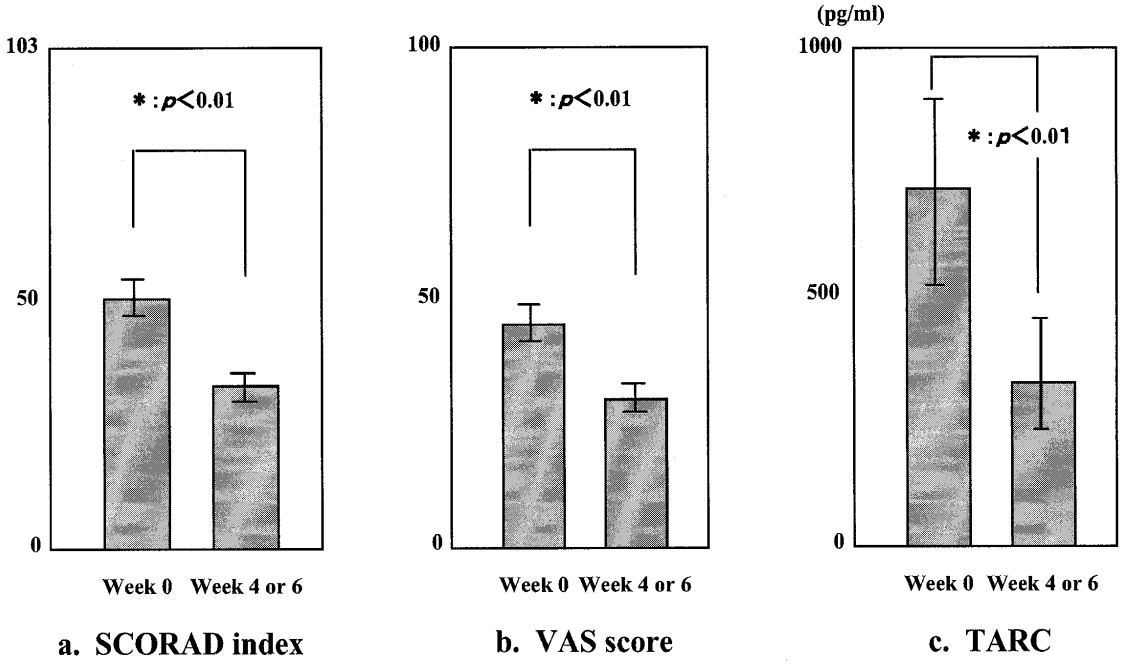

Fig. 1 (a) SCORAD index, (b) VAS score and (c) Serum level of TARC in patients with AD before and after the treatment with KBG.

Mann-Whitney U test and the paired *t*-test. A p-value of less than 0.05 was considered to be statistically significant.

Results and Discussion

The results showed that the SCORAD index and VAS score were significantly decreased by the administration of KBG (SCORAD index 48.84 ± 3.16 versus 32.94 ± 2.30, $p<0.01$; VAS score 48.58 ± 3.32 versus 31.96 ± 3.36, $p<0.01$; Fig. 1a, b).

The serum TARC level of the AD patients before administration of KBG was much higher than that of normal controls as reported previously.[3] The elevated serum TARC level was significantly decreased at week 4 or 6 by administration of KBG. (313.15 ± 85.33 pg/ml, $p<0.01$; Fig. 1c).

In this study, KBG decreased the disease activity of AD as evaluated by SCORAD index and VAS score. Furthermore serum TARC level was also decreased in accordance with the improvement of AD. These results suggest that KBG may improve AD by the inhibitory effect on Th2-type chemokine production. Therefore, it is expected that KBG could be used more effectively to treat inflammatory disease involving Th2-type chemokines, such as atopic dermatitis and bullous pemphigoid.[2]

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Japanese abstract

アトピー性皮膚炎は痒みと湿疹病変を伴う慢性炎症性疾患であり，その急性期には皮膚病変内に多くの Th2 細胞の浸潤がみられる。TARC は CC ケモカインのひとつで，この Th2 細胞に対して選択的な遊走活性を持つ。また，アトピー性皮膚炎患者では血清 TARC 値が正常と比較し有意に上昇しており，さらに重症度と相関することが知られている。一方，駆瘀血剤のひとつである桂枝茯苓丸は，これまで主に血栓症や動脈硬化症の患者の治療に用いられてきた。今回我々はアトピー性皮膚炎患者における疾患活動性と TARC 産生に対する桂枝茯苓丸の作用について検討した。36名のアトピー性皮膚炎患者に 4 ～ 6 週間桂枝茯苓丸を投与し，投与前後で SCORAD index, VAS score を計測しその効果を評価した。また同時に血清 TARC 値も測定した。その結果，桂枝茯苓丸内服前に高値であった SCORAD index, VAS score は，内服後には有意に低下していた。また血清 TARC 値も投与

前は高値であったが，内服後は有意に低下していた。以上の結果より，桂枝茯苓丸はこれまで知られていた作用に加えTARC産生を抑制する可能性が示唆され，アトピー性皮膚炎などTh2ケモカインが関与する炎症性疾患に対して有用な治療法になりうることが期待された。

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