Treatment of Atopic Dermatitis with Immunomodulatory Drugs

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Abstract: Atopic dermatitis is a common, intensely pruritic, chronic inflammatory skin disease that significantly affects the patients’ health and quality of life. Major standard treatments directed at controlling the predominant symptoms of atopic dermatitis, namely, eczematous lesions and pruritus, include topical steroids and antihistamines. However, there are several concerns in regard to the treatment with topical steroids, especially when used long term or on the face and neck. Topical immunomodulators such as tacrolimus ointment represent a new therapeutic option specifically developed for the treatment of atopic dermatitis without the unwanted local side-effects of topical steroids. Systemic immunomodulators such as cyclosporin represent a new therapeutic option developed specifically for the treatment of severe refractory atopic dermatitis resistant to conventional therapies. This article reviews the future role of these immunomodulators in the treatment of atopic dermatitis.

Key words: Atopic dermatitis; Topical steroid; Tacrolimus ointment; Cyclosporin

Introduction

In general, the treatment of atopic dermatitis (AD) can be roughly categorized into treatment (remission) of existent cutaneous inflammation (eczematous lesions) and prevention of new inflammation. It is important to achieve rapid remission of inflammation; when the inflammation is prolonged, skin lesions such as lichenification and prurigo may develop, which are resistant to treatment. In the cutaneous inflammation associated with AD, not only activated T cells (Th2 and Th1), but also other inflammatory cells, such as mast cells, Langerhans cells, and eosinophils are known to be involved in a complex manner. Drugs that inhibit all of these cells could therefore be expected to exhibit prompt therapeutic effects. From this point of view, steroids and immunomodulatory drugs appear to be among the most useful drugs.

Topical steroids are the most effective drugs for achieving a quick remission of inflammation, and have been used for decades. How-
ever, the number of AD patients with local adverse reactions due to long-term use of topical steroids, with intractable AD lesions resistant to topical steroids, and with AD eruptions on the face and neck, where long-term use of topical steroids is difficult, is increasing. As a result, there has been an increasing demand for the development of drugs that exert their anti-inflammatory and anti-allergic actions through different mechanisms from those of steroids.

Under such circumstances, immunomodulatory drugs have been developed to provide a new approach to the treatment of AD. In this article, discussion will be focused on topical FK 506 (tacrolimus), which is an immunomodulatory drug introduced recently for the treatment of AD, and the expected roles of this drug on the treatment of AD in the future.

Role of Steroids and the Problems Associated with These Drugs in the Treatment of AD

The Japanese guidelines for the treatment of AD by pharmacotherapy basically recommend the use of topical steroids for the treatment of eczematous lesions. This is based on the observation of the excellent efficacy of topical steroids in effecting a quick cure in eczema. However, the following precautions are listed for the use of topical steroids: 1) Selection of the type, strength, and amounts of the topical steroids should be based on the severity, location and characteristics of the eczematous lesions, and the patients’ age. 2) As a general rule, the use of topical steroids on the face should be avoided. If it is inevitable, weak preparations should be used for the shortest duration possible. 3) The severity of the lesions should be evaluated every week, and switching of the drug should be considered. As a general rule, only physicians with a good understanding of the characteristics and effects of these drugs should be allowed to prescribe topical steroids.

The problems associated with the use of topical steroids include the occurrence of local adverse reactions, such as skin atrophy, telangiectasia, and hypertrichosis. These may result from long-term use, or use in areas susceptible to local adverse reactions, such as the face and neck.

Therefore, topical drugs that exert similar anti-inflammatory and anti-allergic actions via different mechanisms from those of topical steroids, and that do not elicit the local adverse reactions observed with topical steroids, are urgently needed. It is in this background that topical tacrolimus came to be developed.

Actions of Tacrolimus

In 1984, tacrolimus was discovered as a compound with a macrolide skeleton produced by Streptomyces tsukubaensis. With a molecular weight of 822.05, it is a much smaller molecule than cyclosporin, which exerts similar actions and has a molecular weight of 1202.63. It acts mainly during the early stage of T-cell activation. It accomplishes efficient immunosuppression by inhibiting the expression of cytokine genes, which play important roles in immune responses.

The drug binds to calcineurin, a dephosphorylation enzyme activated in the presence of Ca$^+$ and calmodulin, and inhibits its actions, thereby inhibiting the translocation of a T-cell-specific transcription factor (NF-AT) subunit (NF-ATc) from the cyto-plasma to the nucleus. In this way, the drug is believed to inhibit the expression of such cytokine genes as that of IL-2.1) Therefore, unlike steroids, it does not induce skin atrophy.

The mechanisms underlying the therapeutic actions of tacrolimus on AD are as follows: 1) inhibition of cytokine production and release from Th1 cells and Th2 cells; 2) disruption of the antigen-presenting ability of Langerhans cells; 3) inhibition of IgE-dependent histamine release from mast cells and basophils; 4) inhibition of degranulation of eosinophils; and 5) inhibition of cytokine-induced chemokine production from epidermal cells and fibro-
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A problem associated with this ointment, however, is the high incidence of transient skin irritation symptoms after its application, associated with erythema and a burning sensation, pain, and itching. These symptoms occur at a particularly high incidence when the ointment is used for eruptions on the face and neck.\textsuperscript{5) Most of these symptoms are transient (about 3 or 4 days) and mild or moderate, and disappear immediately upon remission of the eruptions.

Results of Treatment of AD with Topical Tacrolimus

At present, the use of 0.1\% tacrolimus ointment for the treatment of AD in adult patients is covered by insurance in Japan. Its clinical efficacy has been demonstrated to be significantly superior to that of 0.1\% alclometasone dipropionate ointment against eruptions on the face and neck,\textsuperscript{3) and to be almost equivalent to that of 0.12\% betamethasone valerate ointment against eruptions on the trunk and extremities.\textsuperscript{4)}

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However, it is important to explain to the patient in advance about the possibility of appearance of these symptoms of skin irritation with the ointment application.

Another problem associated with this ointment is that topical application of the ointment over an extensive area may lead to elevated blood concentrations of the drug and the risk of occurrence of systemic adverse reactions. In a study in which a total of 20 g/day of 0.1% ointment was used (10 g at a time, an amount sufficient for application over the whole body), a blood concentration of 20 ng/ml was detected in one of 3 AD patients. However, the percutaneous absorption of the drug in this patient decreased as the eruptions remitted, associated with an immediate decrease in its blood concentration. A week later, the blood concentration was found to have decreased to below 4 ng/ml. Thus, the elevated blood concentration associated with the ointment application over an extensive area of the body is transient and believed to be not problematic. However, some precautions must be addressed in patients in whom remission of the eruptions is not achieved even after prolonged high-amount topical use. Precautions must also be addressed when the barrier functions of the skin are markedly impaired, because in such a situation, the systemic absorption of the drug may be markedly accelerated.

In another study in which tacrolimus ointment was applied over the whole body for a prolonged period (observation for more than 12 months), a low concentration of the drug was detected in the blood, although not very frequently, when about 10 g/day was applied topically in patients with severe eruptions. In this study, however, no problematic systemic adverse reactions were reported in any of the 568 subjects examined. Thus, the use of the drug over a limited area or for prolonged periods of time, especially when the eruptions remit within a short period of time, does not appear to be associated with any clinical problems. However, in consideration of safety, the maximal dose of tacrolimus ointment should be limited to no more than 10 g/day.

Another problem is complicating infection. According to clinical studies conducted to date, folliculitis is noted at the highest incidence (about 10%), but the condition remits rapidly with oral and topical administration of antibacterial drugs. The incidence of the infection did not exceed this percentage when the drug was used for prolonged periods.

As to other types of infection, Kaposi’s varicelliform eruptions (KVE) induced by widespread percutaneous inoculation of herpes simplex virus (HSV) was reported at an incidence of 4% in the 568 subjects followed for a prolonged period. The incidence of KVE is believed to have increased in recent years with the increase in number of AD patients, and the condition has become more severe. In a narrow sense, KVE is defined as a condition that is associated with systemic symptoms, including fever, general fatigue and multiple, relatively large blisters. However, conditions with relatively mild symptoms induced by re-infection are also regarded as KVE in Japan (broad definition). The annual incidence of KVE among AD patients in Japan is estimated to be about 7%.

The association between the use of immunomodulatory drugs in AD and the occurrence of KVE is unknown. However, one study suggested an estimated annual incidence of 5.6% in 568 subjects receiving tacrolimus ointment application (incidence of KVE by the narrow definition was about 4%). Therefore, at present, the use of topical tacrolimus does not appear to be associated with an increased incidence of KVE. However, it goes without saying that precautions must be addressed to ensure early detection and early treatment of this condition.

Based on the results of studies on the use of tacrolimus ointment to treat pediatric AD patients, a 0.03% ointment was developed and is now commercially available in the United States. In Japan, clinical studies have been conducted on the use of this ointment for AD in
children (ranging in age from 2 to 15 years). Thus, the use of the drug in children may also be covered by insurance in the near future. Moreover, the development of another macro-lide immunomodulatory drug, topical ascomycin, is under way, although its efficacy may be inferior to that of tacrolimus.

Figure 2 shows the flow chart for the use of tacrolimus ointment in the treatment of AD.

**Combined Use of Topical Steroids and Tacrolimus Ointment**

Topical steroids, especially those with high potency, are known to be useful for achieving prompt remission of the inflammation in AD; however, prolonged use may be associated with local adverse drug reactions, including skin atrophy. Tacrolimus ointment has a relatively limited efficacy, however, it is more suitable for prolonged use. In the clinical setting, it is recommended that these characteristics of the two drugs be used to advantage, and that the drugs be combined to obtain good efficacy. Specifically, it is possible to reduce the skin irritation symptoms induced by tacrolimus ointment by first using relatively high-potency topical steroids for a short period to sufficiently reduce the inflammation, and then switching to tacrolimus ointment to avoid local adverse reactions.

**Treatment of AD by Oral Cyclosporin**

Treatment with oral cyclosporin (maximum dose: 5 mg/kg/day) is covered by insurance in Europe and Canada only in cases with severe intractable adult patients with AD, resistant to conventional treatments, and in whom the condition markedly impairs the patients’ QOL. Its excellent efficacy has been demonstrated, and clinical studies of the drug have been started in this group of patients in Japan. However, considering the potential risk of occurrence of renal dysfunction, increased blood pressure and various diseases associated with persistent immunosuppression with prolonged use of oral cyclosporin, it is recommended that the drug be administered for as short a period as possible, only until treatment by a more conventional approach becomes feasible.

**Conclusion**

When used appropriately, topical steroids are the most effective drugs for the treatment of AD. However, in the case of patients with intractable AD resistant to topical steroids, patients with eruptions on the face and neck, where prolonged application of topical steroids
is difficult, and patients vulnerable to the local adverse reactions to topical steroids, the combined use of topical steroids and tacrolimus ointments is believed to be useful for improvement of the QOL in AD patients.

REFERENCES


