【表 3】薬剤の使用歴

		該当人数	回答人数
インドメタシン外用歴, %	37.9	55	145
インドメタシン内服歴, %	75.9	110	145
抗菌薬内服歴, %	44.1	64	145
ステロイド外用歴, %	61.4	89	145

【表 4】インドメタシン奏効の有無

インドメタシン奏効の有無		該当人数
無効	7.6%	7
有効	58.7 %	61
著効	33.7%	35
合計	100%	104

【Ⅲ】

研究成果の刊行に関する一覧表

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平成23年度　雑誌

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Invited review article

Regulatory T cells in cutaneous immune responses

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ABSTRACT

Regulatory T cells (Treg) are a subset of T cells with strong immunosuppressive activity. In the skin, it has recently been revealed that Treg play important roles not only in the maintenance of skin homeostasis but also in the regulation of the immune responses, such as contact hypersensitivity and atopic dermatitis. Furthermore, the skin plays important roles in the induction of Treg in the periphery. In this review, we will provide an overview of the mechanism of Treg-mediated immunosuppression and discuss the role of Treg in the skin.

Contents

1. Introduction

Regulatory T cells (Treg) are a subset of T cells with strong immunosuppressive activity. Treg were originally identified as $CD4^+CD25^+$ T cells [1,2]. When mice were depleted of $CD4^+CD25^+$ cells, they spontaneously developed autoimmune diseases and allergies, indicating that $CD4^+CD25^+$ T cells are essential for the maintenance of self-tolerance. Later on, the forkhead box p3 (Foxp3) gene was identified as the master transcriptional factor of Treg [3].

There are at least two kinds of $Foxp3^+$ Treg: naturally occurring Treg (nTreg) and inducible Treg (iTreg) [4]. nTreg develop in the thymus, and play an important role in the maintenance of self-tolerance and immune homeostasis. Scurfy mice, which possess a defective *Foxp3* gene, exhibit hyperactivation of $CD4^+$ T cells and overproduction of proinflammatory cytokines, and typically die within a month after birth [5]. Patients with IPEX syndrome (immune dysregulation polyendocrinopathy, enteropathy, X-linked syndrome) have a mutation in the human *FOXP3* gene, and are therefore regarded as the human counterpart of scurfy mice [6]. iTreg, on the other hand, are induced from naïve T cells in the presence of transforming growth factor (TGF)-β, and develop in the periphery. Retinoic acid facilitates the differentiation of naïve T cells to $Foxp3^+$ Treg [7,8] and may be related to the establishment of oral tolerance, although it remains to be determined whether iTreg are functionally stable and to what extent they contribute under physiological conditions.

In addition to $Foxp3^+$ Treg, there are other types of Treg, such as Tr1 and Th3 cells; these are induced in the periphery [4,9,10]. Tr1 cells can be induced through the antigenic stimulation of naïve T cells in the presence of IL-10 *in vitro*, and exert a suppressive effect *in vitro* by inducing large amounts of IL-10 and TGF-β. Th3 cells

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produce TGF-β in an antigen-specific manner, and exert a suppressive effect. Intriguingly, however, both are Foxp3 and CD25 negative. No further details of this population are discussed in this manuscript.

Evidence has accumulated regarding the regulatory roles of Treg not only in self-tolerance, but also in a variety of pathophysiological immune responses, such as gastritis [11], arthritis, encephalomyelitis [12], inflammatory bowel disease (IBD) [13], insulin-dependent diabetes [14] and various allergic skin diseases such as contact hypersensitivity or atopic dermatitis.

In this review, we will provide an overview of the mechanism of Treg-mediated immunosuppression, mainly focusing on $Foxp3^+$ Treg, and discuss the role of Treg in the skin immune responses, focusing on contact hypersensitivity and atopic dermatitis.

1.1. Mechanism of suppression by Treg

Treg potently suppress the proliferation of T cells when Treg are co-cultured with responder cells that have been stimulated with a specific antigen or a polyclonal T cell receptor stimulator *in vitro*. Multiple suppression mechanisms have been proposed based on *in vitro* assays; for example, IL-10 [13], TGF-β [15], and IL-35 [16] have been considered as possible soluble suppressive factors of T cell proliferation. Absorption of IL-2 by Treg may also be involved in inhibiting T cell proliferation [17]. It has also been reported that Treg exert their regulatory functions by cell–cell contact-dependent factors, such as CD39/CD73 [18] and granzyme/perforin [19]. In addition to these direct suppressive effects, Treg indirectly suppress T cell proliferation by affecting the function of APCs. It has been reported that Treg inhibited the T cell stimulatory capacity of APCs by down-regulating CD80 and CD86 expression through cytotoxic T-lymphocyte antigen (CTLA)-4 and lymphocyte function-associated antigen (LFA)-1 [20]. Using two-photon microscopic analysis, Tadokoro et al. [21] and Tang et al. [14] have revealed that Treg inhibit stable contact and interaction between APCs and effector T cells. Treg also stimulate DCs to express the enzyme indoleamine 2,3-dioxygenase (IDO), which catabolizes the conversion of tryptophan to kynurenine, a toxic factor to T cells [22]. In addition to their effect on APCs, it has also been reported that Treg down-regulate mast cell function by suppressing mast cell degranulation and anaphylactic response through OX40–OX40L interaction [23]. The mechanisms by which suppression is achieved may vary depending on context, however, and it has not yet been determined how these *in vitro* findings correlate with *in vivo* suppression.

1.2. Characterization of Treg in the skin

Treg exist in all non-lymphoid tissues; the skin has a particularly high proportion of Treg in the steady state [24–26]. Treg in the skin are $CD44^+$ and $CD103^{high}$ [24–26], and express the chemokine receptors CCR4, CCR5, CCR6 and CCR7. $CCR5^+$ Treg preferentially migrate to cutaneous lesions of *Leishmania major* infection [27]. Mice with a complete loss of CCR4 on Treg develop spontaneous lymphocytic infiltration and severe inflammation in the skin and lungs, accompanied by peripheral lymphadenopathy and increased differentiation of skin tropic $CD4^+Foxp3^-$ T cells. Using α-1,3-fucosyltransferase VII (Fut7) deficient mice, Dudda et al. [26] have reported the importance of E- and P-selectin ligand for Treg migration to the skin. Loss of these selectin bindings caused skin-specific inflammation, indicating the essential role of skin-resident Treg for maintaining immune homeostasis locally.

2. Treg induction and expansion in the skin

Ultraviolet (UV) radiation to the skin is well known to cause immunosuppression, and is accordingly applied as a treatment for a wide variety of skin diseases. Recently, it has been revealed that one of the immunosuppressive mechanisms involved in this effect is mediated by Treg, which are induced by UV irradiation [28]. It has been proposed that the cells responsible for this induction of Treg are epidermal Langerhans cells (LCs), an important group of skin-resident dendritic cells. Loser et al. [29] have reported that the receptor activator of NF-kappaB ligand (RANKL) was induced in keratinocytes by UV exposure, and RANKL-activated LCs were responsible for the development of UV-induced Treg. It has also been reported that the induction of Treg by UV irradiation was completely abolished by the depletion of LCs using Langerin-DTR mice or steroid mometasone [30,31]. In addition, it has recently been reported that IL-10-producing and OX40 ligand-expressing mature LCs are responsible for the induction of Treg upon UV exposure [31], suggesting the importance of LCs for Treg induction. In addition to UV-induced immunosuppression, similar findings were observed concerning the mechanisms involved in immunosuppression during skin grafting. Yoshiki et al. [32] have reported that the development of contact hypersensitivity (CHS) was suppressed when mice were sensitized with a hapten through full-thickness grafted skin. In this model, $CD4^+CD25^+$ but not $CD4^+CD25^-$ T cells in draining lymph nodes (LNs) were responsible for this suppression. In addition, a high expression of RANKL was observed in the grafted skin, and recombinant RANKL stimulated LCs to produce IL-10. These findings suggest that the LCs play important roles in the peripheral induction of Treg. Recently, it has been reported that glucocorticoids modify LCs to produce TGF-β and expand regulatory T cells in humans [33] (Fig. 2), implying that glucocorticosteroids may exert their anti-inflammatory functions by inducing Treg.

The phenotypes and suppression mechanisms of UV-induced Treg are different from those of nTreg. Schwartz et al. [34,35] have reported that the administration of $CD4^+CD25^+$ cells from UV-irradiated DNFB-sensitized mice impaired sensitization of CHS. These UV-induced Treg did not suppress the CHS response when administered before elicitation, though natural $CD4^+CD25^+$ Treg did. Direct injection of UV-induced Treg into the elicitation sites did suppress the CHS response, however. They accordingly concluded that UV-induced Treg did not express skin-homing receptors for E- and P-selectins, and so failed to suppress elicitation. In addition, they reported that UV-induced Treg changed APCs in LNs from a stimulatory to a regulatory phenotype by modulating the co-stimulatory molecules on APCs, which, in turn, further induce Treg [36].

Although the importance of LCs has been suggested as mentioned above, other groups have reported the importance of dermal DCs in UV-induced immunosuppression and peripheral Treg induction. Wang et al. [37] reported the UV-induced immunosuppression was abolished by selective depletion of Langerin-positive dermal DCs, suggesting the importance of Langerin-positive dermal DCs in Treg induction. It has also been reported that retinoic-acid producing CD103-negative dermal dendritic cells have the ability to induce Treg in draining LNs [38], in contrast to the equivalent phenomenon in the gut, where CD103-positive DCs are responsible for the induction of Treg [39].

3. Treg in CHS

CHS, a frequently used mouse model of contact dermatitis, is a prototype of skin immune response, and the role of Treg in CHS has been gradually revealed.

The development of CHS is divided into two phases: sensitization and elicitation [40]. In the sensitization phase, low molecular weight compounds called haptens are cross-linked to epidermal proteins and taken up by resident DCs such as LCs and dermal DCs. Subsequently, these cells are matured by proinflammatory

cytokines such as TNF-α, IL-1β, and prostaglandin E_2, and migrate to the draining LNs to present antigens in a CCR7- and CXCR4-dependent manner [41,42]. After antigen presentation, naive T cells are activated and differentiated into antigen-specific Th1 and Tc1 cells under the influence of polarizing signals such as IL-12 and other chemical mediators [43]. Th17 cells are also involved in the pathogenesis of CHS [44]. When the skin is re-exposed to the same hapten after establishment of the sensitization, an antigen-specific T cell-mediated inflammation that is known as elicitation phase is provoked. Upon re-exposure to the same hapten, keratinocytes and mast cells produce chemokines and pro-inflammatory cytokines such as TNF-α and IL-1β, which activate endothelial cells and induce the expression of E- or P-selectins [45–47]. Then, neutrophils and antigen-specific T cells enter the dermis and release IFN-γ, which further stimulates keratinocytes to induce massive leukocyte infiltration [48].

3.1. Treg in the CHS response – elicitation phase

The effect of Treg on CHS has mainly been investigated in the elicitation phase. Ring et al. have purified $CD4^+CD25^+$ Treg from naïve mice and administered them into TNCB-sensitized recipient mice intravenously one day before elicitation [49]. Administration of Treg significantly suppressed the ear swelling response and inflammatory cell infiltration into the skin compared to those of vehicle-treated mice. Ring et al. have reported that these suppressive effects are mediated by soluble factors, especially IL-10. Administration of a culture supernatant of Treg suppressed the CHS response, and this suppression was reversed by an anti-IL-10 Ab. Furthermore, Treg from IL-10-deficient mice failed to suppress the CHS response by inhibiting the leukocyte influx into the inflamed skin.

The same group has recently reported that the adenosine produced by Treg is involved in blocking the influx of leukocytes into the skin by downregulating E- and P- selectins on endothelial cells [50]. Adenosine triphosphate (ATP) is first degraded by CD39 to adenosine diphosphate (ADP) and then to adenosine monophosphate (AMP). The AMP is serially dephosphorylated by CD73 to adenosine. Treg are strongly positive for both CD39 and CD73 expression; therefore, Treg convert ATP to adenosine and suppress the CHS response. On the other hand, conventional T cells exhibit only a low basal expression level of CD39. Accordingly, injection of adenosine or Treg abrogated the ear-swelling response in CHS, which was not seen using Treg from CD39-deficient mice [50]. Moreover, Treg further upregulate CD39 expression after activation; this activation is a prerequisite for Treg to acquire their suppressive capacity.

3.2. Treg in the CHS response – sensitization phase

While reports on the role of Treg in the sensitization phase have been rather limited compared to those discussing the elicitation phase, some interesting reports have recently been published. Dubois et al. [51], for example, have reported the involvement of Treg in the induction of oral tolerance and inhibition of DNFB-induced CHS. Oral tolerance was induced by feeding DNFB orally prior to DNFB sensitization. Although no such tolerance induction was seen in $CD4^+$ T cell-deficient mice, transfer of naïve $CD4^+CD25^+$ T cells restores oral tolerance in those mice, in a manner independent of IL-10 [51]. The same authors also showed that administration of neutralizing anti-CD25 monoclonal antibody (mAb) impairs oral tolerance in WT mice. Intriguingly, administration of anti-CD25 mAb before sensitization had no significant affect on the ear swelling response, suggesting that $CD4^+CD25^+$ T cells are responsible for oral tolerance induction, while the role of Treg in the sensitization phase remained unclear. Ring et al. have recently reported that the administration of Treg suppressed the extent of sensitization in CHS by inhibiting DCs and CD8 T cells in the draining LNs [52]. In their report, Treg and DCs established gap junctions, which caused a reduction in the capacity of DCs to stimulate CD8 T cells. In their next report, the same authors stated that Treg activation in draining LNs was mediated by ATP, because Treg acquired an activated phenotype upon ATP treatment *in vitro*, while blockage of ATP receptors on Treg abrogated ATP-mediated activation and suppressive function of Treg *in vivo* [53].

3.3. The role of endogenous Treg in CHS

As described above, exogenous administration of Treg suppresses CHS both in the sensitization phase and in the elicitation phase. It remains unclear, however, whether endogenous Treg play the same suppressive role under physiological conditions. To this end, specific depletion of Treg *in vivo* is required. Although $CD4^+CD25^+$ has been used as a marker for Treg, CD25 is expressed in activated CD4 cells as well as in Treg. Therefore, Foxp3 is a more definitive marker of Treg, but because Foxp3 is a transcriptional factor that exists intracellularly, the purification of live Treg or depletion by means of neutralizing mAb has been technically difficult.

To solve these problems, Foxp3 reporter mice expressing human CD2 and human CD52 chimeric protein have been generated and designated as $Foxp3^{hCD2/hCD52}$ mice. Since $Foxp3^+$ cells co-express hCD2 on the cellular surface, live $Foxp3^+$ Treg are sorted with anti-hCD2 mAb and depleted with neutralizing anti-hCD52 Ab [25]. The mice have been used in the investigations into the role of endogenous Treg in CHS. Depletion of Treg in the elicitation phase caused the ear swelling response to be enhanced and prolonged compared with that seen in the control, indicating that Treg is responsible for terminating skin inflammation in CHS [25].

In addition, the role and mobility of Treg in the skin during CHS was investigated. Kaede-transgenic mice are genetically engineered to ubiquitously express Kaede protein, a photoconvertible protein that changes its fluorescence from green to red under exposure to violet light. Therefore, mobility of cells from the skin under physiological conditions can be analyzed. Treg were found to localize abundantly in the inflamed skin seen in CHS, and these skin Treg were found to migrate further back to draining LNs. Treg from the skin showed significantly higher mRNA expression of T cell suppression-associated molecules such as IL-10, TGF-β and CTLA4. Consistently, Treg from the skin exhibited significantly stronger suppressive activity both *in vivo* and *in vitro* (Fig. 1). These results suggest that Treg in the skin also play important roles in the termination of dermatitis and possibly in the control of systemic immune responses.

It has been suggested that Treg in the skin contribute to its homeostasis, since chronic depletion of skin Treg leads to the development of spontaneous dermatitis [24,26]. Schneider et al. have reported that CCR7-deficient mice showed a reduced number of Treg in draining LNs and an enhanced inflammatory response in CHS after repeated hapten application [54], which suggests the homing of Treg to draining LNs through CCR7 plays an important role in eliciting the function of Treg.

Endogenous Treg regulate the extent of sensitization as well as that of challenge in CHS. Depletion of Treg during the sensitization phase leads to enhanced skin inflammation [55]. Mice depleted with Treg population showed increased numbers of memory T cells and higher expression levels of costimulatory molecules in DCs in draining LNs compared with control mice, suggesting that endogenous Treg modulate DC function and thus regulate the extent of sensitization [55]. Recent findings on the role of Treg in

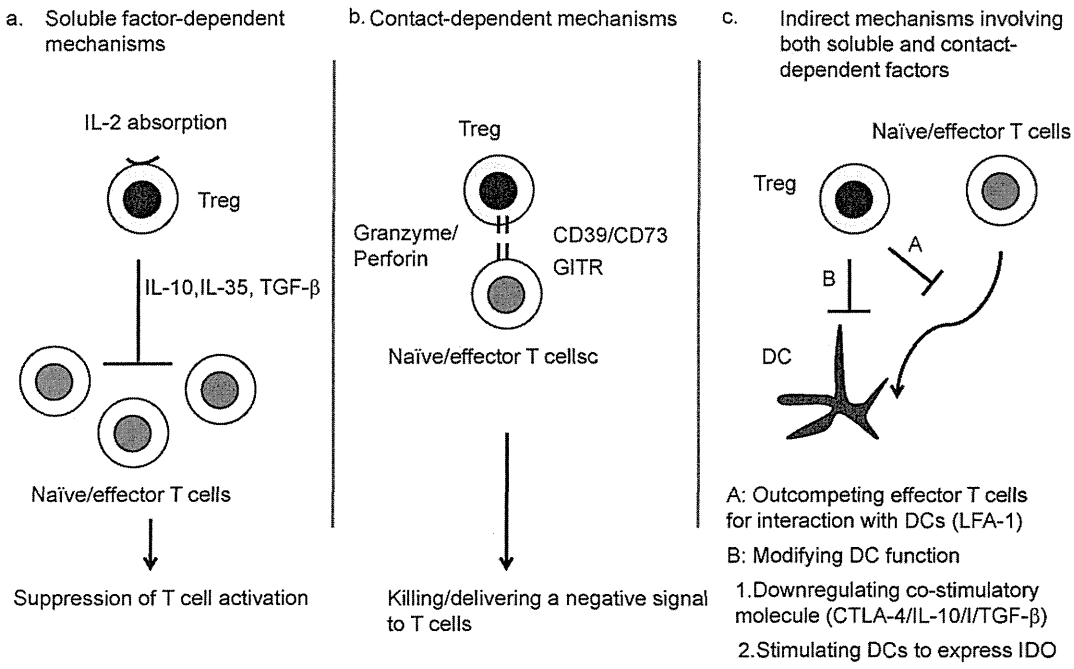

Fig. 1. Possible mechanisms involved in suppression by Treg. (a) Soluble factor-dependent mechanisms. Treg produce large amounts of IL-10, IL-35, and TGF-beta, all of which suppress naive/effector T cell activation. Treg also absorb IL-2, which causes cytokine deprivation-induced apoptosis among effector T cells. (b) Contact-dependent mechanisms. CTLA-4 on Treg deliver negative signals to T cells. CD39/CD73 on Treg catalyze ATP and generate pericellular adenosine, exerting an anti-inflammatory effect. Treg also may kill responder T cells by a granzyme or perforin-dependent mechanisms. (c) Indirect mechanisms. Treg inhibit the interaction between DCs and effector T cells. Treg also downregulate DC activation and thus cause immunosuppression.

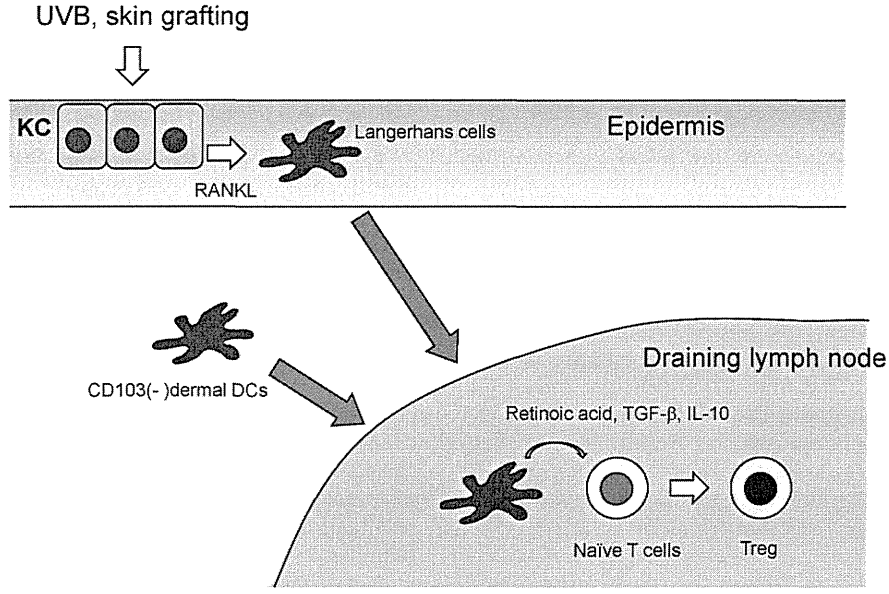

Fig. 2. Proposed mechanism of Treg induction by skin DCs. UV exposure or skin grafting induces RANKL expression on keratinocytes, which stimulate LCs. RANKL-stimulated LCs then induce Treg in draining LNs. Under conditions of UV exposure, it has also been proposed that the UV-induced Treg affect DCs and modify their functions from a stimulatory phenotype to a regulatory phenotype, which further induces Treg. In addition to LCs, CD103-negative dermal DCs can induce Treg in draining LNs.

CHS are summarized in Table 1, and schematic views of those findings are illustrated in Figs. 3 and 4.

4. Atopic dermatitis (AD) and Treg

Atopic dermatitis is one of the most common skin inflammatory disorders. New insights point to an important role of structural abnormalities in the epidermis combined with immune dysregulation [56]. Although studies on the role of Th2 cells have focused on the pathophysiology of AD, recent reports have indicated the importance of other T cell subsets such as Th17 [57] and Treg.

Ou et al. [58] have compared the numbers and functionality of peripheral blood mononuclear cells (PBMC) between healthy controls and AD patients, and reported that AD patients have higher numbers of Treg, each with a suppressive activity comparable to that of Treg in healthy controls, in the peripheral blood. Others have also reported that increased numbers of Treg in the PBMC of AD patients [59] and expansion of Treg were positively associated with disease activity in AD [60]. On the other hand, it

Table 1
An overview of recently published papers about Treg and CHS.

	Major findings	Reference
Sensitization	Attenuated sensitization by Treg induced by RANKL-activated LC in a UV-immunosuppression model	[29]
	Attenuated sensitization by Treg induced by IL-10 from RANKL-activated LC in a skin graft immunosuppression model	[32]
	Attenuated sensitization by Treg induced by orally administered antigen in an oral tolerance model	[51]
	Treg attenuate sensitization by modifying DC function through gap junction formation	[52]
	Treg acquire an activated phenotype by means of ATP in draining LNs	[53]
	Enhanced ear swelling response resulting from the depletion of endogenous Treg	[55]
Elicitation	Reduced ear swelling response resulting from the inhibition of the leukocyte influx through IL-10 from Treg	[49]
	Reduced ear swelling response resulting from the inhibition of the leukocyte influx through adenosine from Treg via CD39/CD73 (inhibition of E- and P-selectin expression in endothelial cells)	[50]
	Treg acquire activated phenotype by means of ATP in blood.	[53]
	Enhanced and prolonged ear swelling response resulting from depletion of endogenous Treg	[25]

has also been reported that the numbers of Treg among the PBMC are similar between AD and healthy controls [61]. In AD skin lesions, it was initially reported that Treg were absent, while Tr1 were detected [62]. Later on, however, several groups reported the existence of Treg in AD skin lesions [63,64]. Because AD is a chronic inflammatory disease with multiple disease stages and multiple factors, and because some treatments for AD such as cyclosporine [59,61,65], glucocoriticoids [33] and UV radiation [28], can alter the number of Treg in the PBMC, the interpretation and comparison of these studies will require careful attention.

Based on observations of IPEX syndrome patients, who show atopic-like dermatitis and high IgE levels, however, it seems probable that the number of Treg is related to the development of AD lesions [6]. As for the function of Treg in AD, it has been reported that their suppressive activity is similar to that of Treg in healthy controls [58]. Reefer et al., however, have reported that a new subtype of Treg with Th2-promoting ability has been observed in AD and that its functions depend on the expression of CCR6 [66]. In this report, CCR6-negative CD25-high positive Treg produced Th2 cytokines, and co-culture with effector T cells selectively enhanced IL-5 production, suggesting the heterogeneity of Treg in AD.

5. Psoriasis and Treg

We will discuss the recent findings about the role of Treg in psoriasis, another common chronic inflammatory skin disease. Although its pathological mechanism is still not completely clear, studies of immune-targeted therapies established it as a primarily immune-mediated disease, such as by Th17, Th1 and Th22 cells, which eventually causes epidermal abnormality [67]. Besides such effector T cells, a substantial number of Treg are detected in lesional skin of psoriasis, and the number of Treg in the psoriatic skin lesion is higher than that in healthy or uninvolved skin [68–70]. The number of Treg in peripheral blood of psoriasis patients is also increased [71], and this increase is positively correlated with the disease activity [68,71]. An anti-TNF alpha antibody infliximab, which has significant therapeutic effects on psoriasis, affects the number of Treg in peripheral blood [72]. It is also suggested that vitamin D metabolite $1,25(OH)_2D_3$ analogs, a successfully used topical treatment for psoriasis, can increase the number of Treg by modulating the function of LCs [73].

Recently, dysfunction of Treg has been reported in psoriasis patients [74]. Treg in both lesional skin and blood from psoriasis

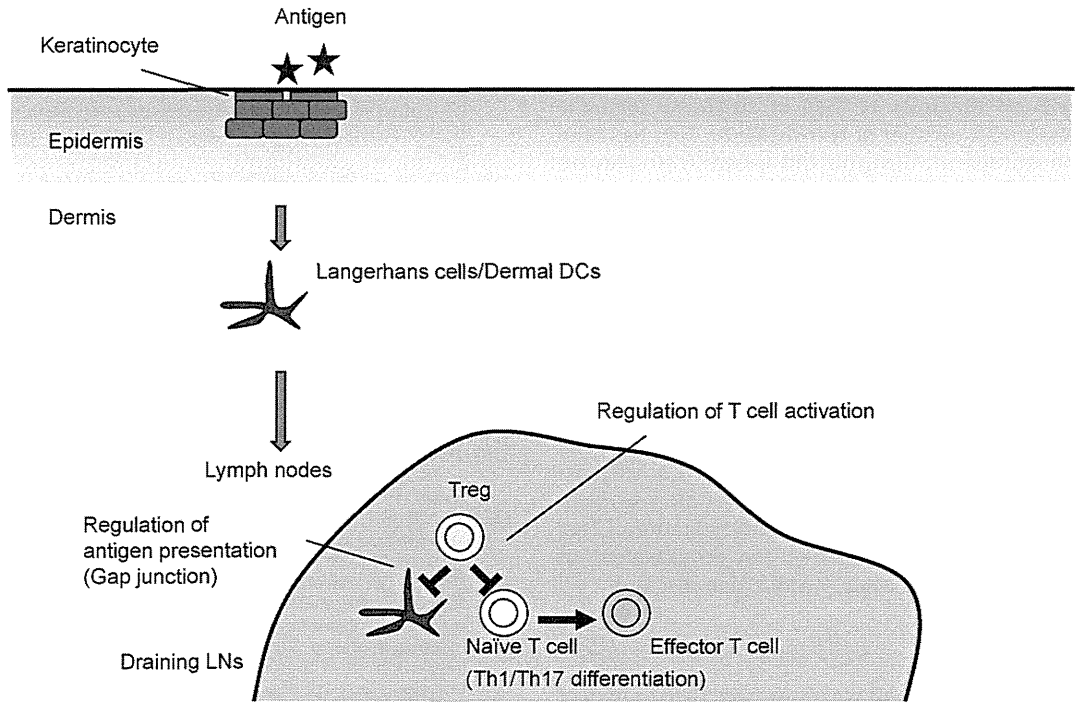

Fig. 3. Possible mechanism of suppression by Treg in sensitization phase of CHS. Treg are activated in draining LNs by ATP. They down-regulate DC activation through gap junction formation and subsequent T cell proliferation, which controls the extent of sensitization.

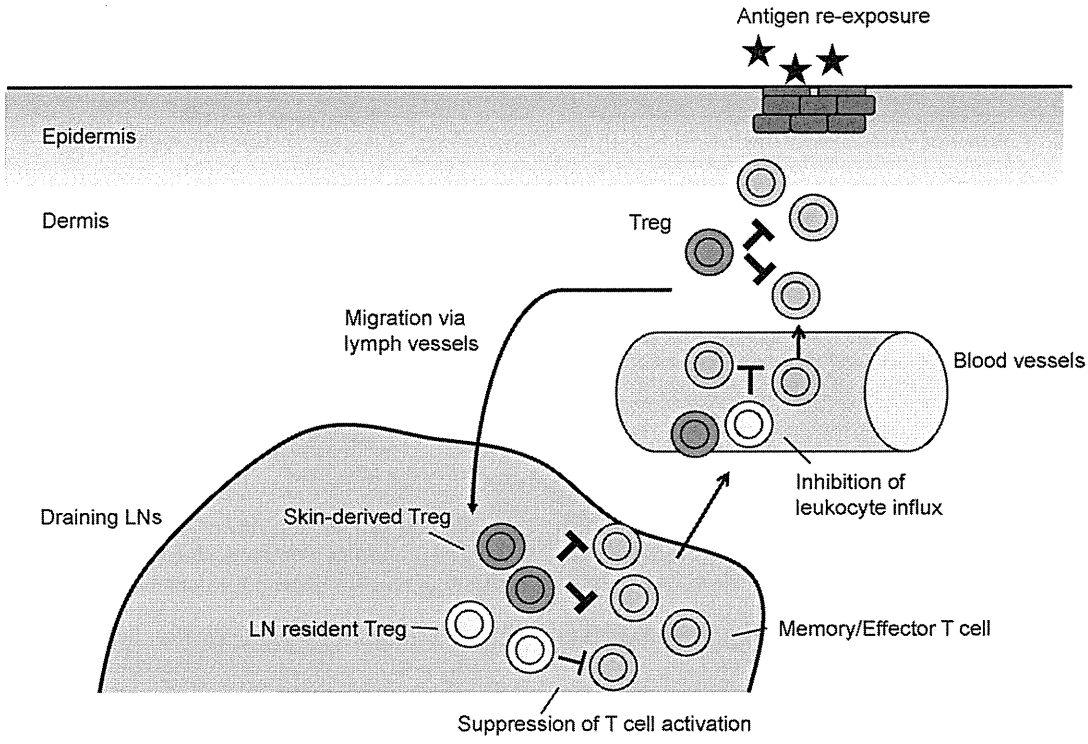

Fig. 4. Possible mechanism of suppression by Treg in elicitation phase of CHS. Treg suppress effector T cells in the LNs and inhibit leukocyte influx into the periphery through IL-10 or CD39-dependent mechanisms. In addition, Treg migrating into the skin could suppress the effector T cell functions in the skin. Furthermore, a fraction of Treg in the skin migrate back to the draining LNs through afferent lymphatic vessels, and can return from there to the skin. These skin-derived Treg possess higher suppression activity than LN-resident Treg, and contribute to the termination of skin inflammation.

patients showed reduced suppressive activity compared with those from healthy donors [74]. Later on, it has been reported that such a Treg dysfunction is caused by IL-6 signaling, which is abundantly produced in psoriasis lesion [75], and that IL-6 enables effector T cells to escape from Treg-mediated suppression both in mice and in humans [74,76,77]. Therefore, the local cytokine milieu may further lead to subsequent hyperproliferation of pathogenic T cells in psoriasis skin and enhancement of disease activities.

6. Conclusion

We have reviewed the roles of Treg in cutaneous immune responses. A considerable amount of knowledge on Treg has been accumulated, and multiple mechanisms and various molecules are reported to be involved in Treg-mediated immunosuppression. It is likely that the suppressive mechanisms of Treg may differ depending on disease stage and the skin immune response type. Analysis using Foxp3-diphtheria toxin receptor knockin mice or $Foxp3^{hCD2/hCD52}$ mice, which enable us to deplete Treg conditionally and specifically, will further reveal the molecular mechanisms and physiological functions of Treg in cutaneous immune responses.

It is crucially important to clarify how and to what extent those molecules are involved in Treg function in humans. From a clinical perspective, the precise mechanism by which Treg function in the elicitation phase is an important issue to be addressed, since most patients with cutaneous immune disease have already been sensitized. We expect that further effort in the investigation of Treg will give us important clues supporting the development of innovative therapeutic approaches for various skin diseases.

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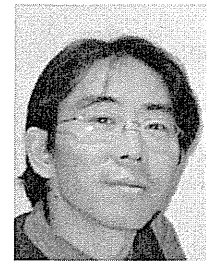

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Acne Management in Japan: Study of Patient Adherence

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Key Words
Acne · Adherence · Japan · Risk factors

Abstract
Obtaining good adherence to acne therapy is a challenge for all dermatologists. We studied 428 acne patients in Japan to determine the likelihood of good adherence and factors associated with medication-taking. This study utilized a simple validated questionnaire to assess risk of poor adherence; information about patient and treatment characteristics was also collected. There was an overall rate of poor adherence in 76% of subjects. Adherence to topical medication was poor in 52% of those treated with a topical agent only (n = 123). Among those taking combination therapies (n = 275), adherence to the topical portion of therapy was poor in 49% of subjects. The likelihood of poor adherence to oral medication was higher, both when administered alone (n = 30, 93% poor adherence) and when given as part of a combination regimen (n = 275, 86%). Factors with an impact on adherence included satisfaction with treatment (p = 0.023) and the experience of side effects (p = 0.027). Patients who felt they had a good understanding of acne and its treatment were more likely to have good adherence. These data suggest that there is significant room for improvement in acne adherence in Japan, as in other areas of the world, and that improved education may enhance adherence.

Introduction

Medication adherence is very important to the success of acne management [1]; however, many factors conspire against this. Acne improvements often occur relatively slowly and it is typically a long-lasting disease that requires prolonged treatment. It is a condition that commonly affects adolescents, who may quickly become frustrated with treatment and have difficulty fitting treatment regimens into their daily routine. Costs of acne therapy and side effects can also negatively impact adherence to acne medications. Failure of over-the-counter products can lead patients to incorrectly believe that effective treatment is not possible. Yet acne is known to be associated with negative psychological effects and it can and should be treated. Thus, clinicians face the challenge of understanding acne adherence and continually working to devise strategies to improve it.

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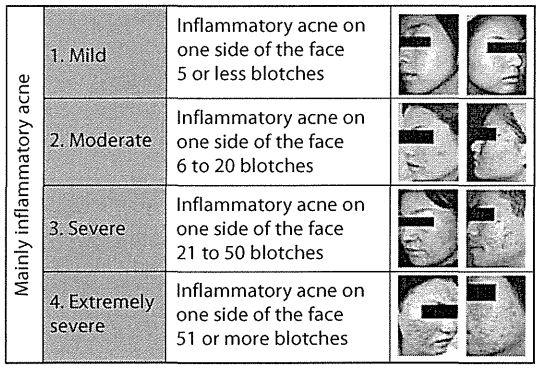

Fig. 1. Criteria to determine the severity of acne vulgaris. Reproduced with permission from [11].

Some studies have evaluated adherence to acne medications in various parts of the world [2–8]; however, there are few data specific to Japan. This study was designed to assess adherence among acne patients in Japan, to determine if there are differences in adherence based on type of treatment (topical or oral), and to evaluate the factors that can affect adherence to acne treatment.

Acne experts and guidelines emphasize that most patients with acne should be managed with a topical retinoid, often in combination with an antimicrobial agent [9, 10]. Expert recommendations stress the importance of topical retinoids in acne therapy [10]; adapalene recently became the first topical retinoid introduced into the market in Japan. Because acne therapy is rapidly evolving in Japan, we considered the timing good for a study of medication adherence. This information may help to guide physicians in treating their patients and, ultimately, to improve patient outcomes and satisfaction.

Methods

This multicenter observational study utilized self-completed and dermatologist-completed questionnaires to assess medication adherence among individuals visiting 59 dermatology clinics throughout Japan between January and March 2010. The dermatology clinics were members of a panel established by the healthcare marketing research agency conducting the study. A secondary objective was to determine factors that had an impact on acne treatment.

Subjects included acne patients undergoing treatment who had a medical consultation for acne ≥1 month to ≤3 months prior to the study consultation. Consecutive patients meeting these criteria had the study explained to them, and were offered the opportunity to participate if they completed an informed consent form. All patients had acne therapy prescriptions, which could have been initiated, changed, or re-instituted at the previous visit. Tolerability of treatment was assessed by the investigating dermatologist and a question on the patient-completed questionnaire. Acne severity at the beginning of the study period was assessed using the Severity Criteria of Acne Vulgaris rating used by the Japanese Dermatological Association [11] (fig. 1).

The likelihood of adherence was assessed using the ECOB Adherence Questionnaire created and validated by Pawin et al. [3]. ECOB assesses the patient's ability to remember 4 key aspects of acne therapy with similar but separate questions for topical and oral therapy; inability to name/describe treatment or 1 response suggesting the patient had not used treatment as directed indicates a likelihood of poor adherence. The ECOB tool was validated against dermatologist prescriptions by Pawin et al. [3]. Quality of life was assessed by the Japanese version of the Dermatology Life Quality Index (DLQI) [12].

Questionnaires were tabulated and analyzed using simple descriptive statistics. Also, the relationship between the objective variable (ECOB adherence assessment) and explanatory variables was examined by the χ^2 test. Explanatory variables included age, age at onset of acne, parents with experience of acne, DLQI overall score (degree of impact on life), consultation with other physicians prior to treatment at current facility, knowledge about acne, degree of satisfaction with current treatment, prescription of acne medications (stratified by which type of medication), period of treatment, experience of side effects, change in acne severity (comparison of severity at consultation prior to the current visit and the current visit), guidance other than drug therapy (such as private preparations and cosmetics), acne scarring seen at the current consultation, and improvement in acne at current consultation in the investigator's opinion. The odds ratio and 95% CI for each explanatory variable was calculated by multiple logistic regression analysis and the results were examined by Wald χ^2 test. The level of statistical significance is 5%.

Results

Study Population

A total of 59 dermatologists participated and recruited 428 acne patients (64% female, 36% male). The mean age of the patients was 24.4 years and females were older than males (mean 25.5 vs. 22.2 years, respectively). Among females, 49% were aged 25 years or older; in contrast, 25% of males were 26 years or older. Most males were aged 16–20 years (39%). A total of 81% of subjects reported not smoking and 62% indicated they consumed alcohol never or rarely. A summary of acne characteristics is shown in tables 1 and 2. Almost all patients (97%) had acne on the face, 11% on the neck, 8% on the chest, 5% on the back and 1% on another body location. Involvement on non-facial areas was more likely with increasing acne severity.

Notably, 42% of subjects had acne scarring. Scars were more likely with increasing disease severity, and were

Table 1. Acne characteristics of the study population (n = 428)

	Overall (n = 428)	Male (n = 153)	Female (n = 275)
Age at onset of acne (mean), years	14.9	15.2	14.8
Age at first acne consultation (mean), years	19.3	18.3	19.9
Parents with acne, %	41	36	44
Acne severity, %			
Mild	20.3 (n = 87)	15	23
Moderate	55.1 (n = 236)	58	54
Severe	20.8 (n = 89)	22	20

Table 2. Chronic vs. relapsing acne in the subgroup aged 25 or older (n = 189)

	Overall (n = 189)	Male (n = 45)	Female (n = 144)
Had no period of time without acne since onset, %	40	47	38
Had a period of time without acne since onset, %	58	51	60

present in 24% of those with mild acne, 42% of those with moderate acne, and 63% of those with severe acne.

Most patients (75%) had not consulted a medical professional for acne prior to the study period. Among those who had consulted a medical professional (n = 109), the length of time between that consultation and the dermatologist consultation was estimated to be greater than 1 year in 38% of cases.

Medications Used for Acne

Information was collected about treatment during the relevant period (at least 1 month and within 3 months after prior consultation for acne). The majority of subjects were prescribed a combination of topical and oral medications (n = 275, 64%), 29% (n = 123) had topical only and 7% (n = 30) had oral only. The mean duration of current treatment was 8.0 weeks. A large majority of subjects (83% topical and 81% oral) had some out-of-pocket medical costs for acne medications and a minority (16% topical and 13% oral) had no out-of-pocket costs.

Topical acne medications were prescribed for 93% (398/428) of the subjects. Topical retinoid therapy was prescribed in 47% of cases, with a higher likelihood of use in males (54 vs. 44%, respectively). Topical antibacterial agents were prescribed in 81% of cases, with a lower likelihood of use in males (75 vs. 84%). The use of topical retinoids increased with increasing severity of acne (from 40% in those with mild acne to 52% in those with severe acne).

Oral medications were prescribed for 71.3% (305/428) of subjects, with oral antibacterial agents being the most frequent systemic medication (79%) followed by vitamins (47%), traditional Chinese medicine (14%), and 'other' (10%). Males were more likely to be treated with an oral antibacterial than females (85 vs. 76%, respectively). The frequency of oral antibacterial use increased with increasing acne severity (from 65% in those with mild acne to 84% in those with severe acne).

In general, subjects indicated that acne medications were well tolerated, with no particular side effects reported among 77% of those using topical medications and 97% of those using oral medications. Procedures were used very infrequently, with the most common being physical removal of comedo (8%) and chemical exfoliation, light therapy, other cosmetics, laser therapy, prescription of private preparation, or other were used in <4% of the group.

Change in Acne

The severity of acne at the study consultation was compared to the severity at beginning of treatment. Overall, acne improved in 46% of patients, did not change in 50%, worsened in 1%, and was unknown in 4%. Improvement was more likely with increasing acne severity (11%