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Atopic Dermatitis: an Update and Review of the Literature

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INTRODUCTION

Atopic dermatitis (AD) (eczema) is a chronically relapsing inflammatory skin disease associated with erythema, scaly and oozing plaques on the forehead and face, neck, hands and flexural areas and severe pruritus (1, 2). AD affects 2-5% of the general population, with ≥ 10 -20% occurrences in infants and children and 1-3% in adults (3). There is a wide variation in the prevalence of AD in different populations of the world, and it appears to be increasing (4, 5). Eczematous skin changes (infantile eczema) of early childhood may differ from common atopic dermatitis in terms of lack of family background of atopy, absence of signs of type I allergies, clinical course, and failure to respond promptly to topical treatment.

Self-healing, the susceptibility to allergy, as well as the characteristic immune profile of lesional skin and peripheral blood are all hallmarks of AD. They together with the 2 different types of AD, the intrinsic and extrinsic types require new definitions and reassessment. According to the recent findings of a search for susceptibility genes, it appears that nonatopic dermatitis should be considered as a distinct entity of childhood eczema. The affected youngsters show dry ichthyosiform and eczematous skin changes at an early age with absence of sensitization to common allergens (6), and 33% of them should complete clearing within 5 years of age.

The optimal protocol for their management has still not been established (7). The diagnostic criteria recommended by the American Academy of Dermatology at the 2003 consensus conference are currently used by many clinicians for diagnosis and treatment of children and adults (8-10). Moreover, the mechanisms underlying the pathogenesis of AD remain unclear, although numerous studies have demonstrated the integral involvement of immunopathology, genetic predisposition, and emotional and environmental stimuli in AD development and progression (8). With the intent of bringing uniformity to the diagnosis of AD, Hanifin and Rajka (11) proposed a number of diagnostic criteria based on their clinical

experience. Williams et al. (12, 13) coordinated a UK working party and refined Hanifin and Rajka's criteria for AD, which were suitable for hospital and epidemiological settings. De et al. (14) found statistical advantage in favor of Hanifin and Rajka's criteria (sensitivity 96.4%, specificity 93.75%) compared to the UK working party's diagnostic criteria (sensitivity 86.14%, specificity 95.83%) that reached a level of significant of <0.005 . They noted that dermatitis in classical distribution, its chronic relapsing nature, dry skin and infra-orbital folds had relative values and these features were helpful in discriminating cases of AD from controls.

Terminology of AD is controversial, with many different names in different countries, among them neurodermitis, constitutionalis atopica, and atopic eczema. Johansson et al. and the European Academy of Allergology and Clinical Immunology (EAACI) (15) proposed a new term "atopic eczema/dermatitis syndrome" (AEDS) which was divided into non-allergic and allergic types, the latter applying to IgE-associated allergic AEDS. They revised the nomenclature of AD and atopy and called only the IgE-associated forms of the diseases true AD (16). It is hoped that the term "eczema" will replace the current term AD.

Several genetic analyses have identified different chromosome regions with a linkage to AD features: Th2 cell cytokine genes on 5q31-33, on 1q21, 3q21, 17q25 and 20p which are closely with some major psoriasis loci (17,18). Further genetic regions associated with AD features include gene polymorphisms, activator of transcription (STAT)-6, the proximal promoter of regulated on activation, normal T-cell expressed and secreted (RANTES), interleukin (IL)-4, IL-4 $R\alpha$ and transforming growth factor (TGF)- β (5, 19, 20, 21). An association of one region in tron 2 polymorphisms (rs 324011) with total serum IgE and a STAT 6 risk haplotype for elevated IgE in white adults was also proven (21). Candidate genes found in regions (3q21, 5q31-33 and 11q13) code for various immunomodulators, including costimulatory proteins (CD80 and CD86) involved in T-cell activation (3q21), IL-3, 4, 5, 11,

and GM-CSF (5q31-33) and beta subunit of the high affinity IgE receptors (11q13) (8).

Finally, a genetic linkage was shown to contribute to immunologic abnormalities of AD pathogenesis (22).

Immunologic background

Skin lesions in AD result from disturbed cellular immunity, including epidermal Langerhans cells (LCs) with IgE receptors of high and low affinity and humoral factors (increased production of IgE and collaboration with Th subsets and LCs, with resultant high production of related cytokines). There are activated Th1 cells with increased production of IFN γ in acute AD skin lesions binding to keratinocytes and, consequently, inflammatory skin changes in the disease (22). A relative imbalance between Th1 and Th2 subsets of CD4+ T cells producing cytokines are indicative of prominent immune disorders in AD (22).

Autoreactivity to human proteins in patients with AD has been postulated as a decisive pathogenetic factor for AD. Several investigations have looked into the question of whether the stress-inducible enzyme, manganese superoxide dismutase (MnSOD) of human and fungal origin, might act as an autoallergen in AD. Schmid-Glendermeier et al. (23) investigated 69 AD patients with SCORAD 27 and demonstrated that human MnSOD may play a role as an autoallergen in a subset of these patients, including those with nonatopic eczema. The authors showed that such sensitization may be induced primarily by exposure to environmental fungal MnSOD of *Malassezia sympodialis* by molecular mimicry leading to cross-reactivity (23).

Genetic and environmental factors play a pivotal role in triggering AD. Research has focused on patterns of cytokines and chemokines reflecting a deviated immune response in AD and on the involvement of various cells and the epidermal barrier. The findings on T cells with regulatory features as well as on IgE-mediated autoreactivity will give insight into the defective tolerance of AD patients (24).

Imbalance of Th1 and Th2 in AD depends on polymorphism in the IL-18 gene on peripheral mononuclear cells, which reacts after stimulation with superantigens through upregulation of IL-18 and downregulation of IL-12 (24). Substance P, “nerve growth factor” (NGF) and vasoactive intestinal polypeptides (VIP) are increased in the blood of AD patients. Cytokines and chemokines are also key factors in the pathogenesis of AD. There is a Th2 cytokine profile of IL-4, IL-5 and IL-13 in the skin in the acute phase of AD, while Th1/0 with IFN γ IL-12, GM-CSF prevail in the chronic phase. Moreover, eosinophilic cationic protein (ECP) and IL-16 are elevated in the acute AD phase, and IL-10 plays an important immunoregulatory role in atopic as well as in nonatopic eczema (24). In lesional AD skin, there are two types of the high-affinity receptors for IgE-bearing myeloid dendritic cells (DC), i.e., LCs and inflammatory dendritic epidermal cells (IDECs), each of which displays a different function in the pathophysiology of AD (10). Specifically, LCs play a predominant role in the initiation of the allergic immune response and conversion of prime naïve T cells into the T cell of the Th2 type with high amounts of IL-4. Furthermore, stimulation of high-affinity receptors for IgE on the surface of LCs by allergens induces the release of chemotactic signals and recruitment of IDECs and T cells in vitro. Stimulation of Fc γ RI on IDECs leads to the release of high amounts of proinflammatory signals, which contribute to allergic immune response.

Keratinocytes play a role in innate immunity by expressing toll-like receptors and by producing antimicrobial peptides in response to invading microbes (25). AD keratinocytes secrete a unique profile of chemokines and cytokines. Apoptosis of keratinocytes is a crucial event in the formation of eczema (spongiosis in AD). The expression of different immunologic parameters have been studied in AD patients since immune dysregulation is a possible key defect in AD. Regulatory T cells (Tregs) or Th3 cells (CD25+/CD4+) can suppress Th1 as well as Th2 cells. Superantigens of *S. aureus* cause defects in Tregs function

and promote the skin inflammation (24). Autoallergens (e.g. Homs 1-5 and DSF 70) are atopy-related autoantigens (ARA) in the setting of AD and other atopic diseases. IgE autoreactivity appears very early (during first year of life) and is associated with the flares in AD. Adhesion molecules may play an important role in the homing of T-cell subsets into allergen-exposed skin of atopic individuals. High expressions of adhesion molecules, especially ICAM-1 and ICAM-3, E-selectin, and L-selectin, in skin lesions of AD patients revealed that they may play an important role in the pathogenesis of AD and may be of clinical relevance for the management of AD. It is important not to ignore various molecules expressed on LCs, such as E-cadherin, a homophilic adhesion molecule, and others (26).

AD is product of an interaction between various susceptibility genes, host and environmental factors, infectious agents, defects in skin barrier function and immunological responses (27). Activation of T lymphocytes, DCs, macrophages, keratinocytes, mast cells and eosinophiles are characteristic of AD skin inflammatory responses (10).

Histopathology

Clinically unaffected skin in AD is still not normal. It has a greater irritant skin response than healthy skin with microscopically sparse perivascular T-cell infiltrate, eosinophiles and macrophages (26). There is marked infiltration of CD4+ activated memory T cell, of LCs (to a lesser extent), of IDECs, and of macrophages in lesional acute AD skin lesions. In chronic AD skin lesions is a chronic inflammation with increased collagen deposition in the dermis, and macrophages dominate in the dermal mononuclear cell infiltrate with eosinophils and smaller numbers of T cells (10, 26).

IgE and IgE receptors

Serum IgE levels are elevated in about 80% of adult AD patients, who also show sensitization against air-borne and food allergens and/or concomitant allergic respiratory allergy (10, 28). The subtype of AD with normal serum IgE levels has a late onset (>20 years

of age) and a lack of these sensitizations. Some of these patients, however, have IgE sensitization against microbial antigens (*Staphylococcus aureus* enterotoxins and *Candida albicans* or *Malassezia sympodialis*) with low IgE serum levels and without any detectable sensitizations. These cases develop into the extrinsic variant of AD with increasing IgE serum levels and sensitizations against air-borne and food allergens later in life.

Expression of high-affinity IgE receptor (FcεRI) can be found in the epidermal skin lesion of patients with AD because of higher IgE-binding capacity of the DCs in their skin and blood (10).

Skin barrier dysfunction

AD is characterized by dry skin and increased transepidermal water loss even in non-lesional skin, and fewer ceramides in the cornified envelope of lesional and non-lesional skin are found AD patients (10, 29). Changes in the stratum corneum pH in AD skin may impair lipid metabolism in the skin. Such alterations allow penetration and susceptibility of irritants and allergens, triggering the inflammatory response, cutaneous hyper-reactivity, inflammation and skin damage characteristic of AD (10). Filaggrin deficiency leads to mild or severe ichthyosis vulgaris and impaired keratinocytes differentiation and barrier formation allow increased transpidermal water loss, and entry of allergens, antigens, and chemicals from the environment in AD (30).

Diagnosis

Well-defined diagnostic criteria are important in the diagnosis of AD and diagnostic criteria developed by Hanifin and Rajka (11) are widely accepted. Skin biopsies are not essential for the diagnosis but they can exclude other diagnosis in adults. In The differential diagnosis, combination forms with components of atopic, contact, and irritative eczema are important. Atopic eczema of the hands and the feet must be differentiated from psoriasis, from keratodermas in the palms and soles and from tinea. The differential

diagnosis of acute AD with intense erythema of the skin, together with exudation or blistering, for example, differs from differential diagnoses of the chronic lichenified form.

Diagnostic tests

The investigation of exacerbating factors in AD involves a patient history, specific skin and blood tests, and challenge tests, depending on the degree of the disease severity and on the suspected factors involved. The APT was introduced to assess sensitization to inhalant allergens in AEDS patients. Fuiano and Incorvaia (31) recently confirmed the high value of APT in patients with mite-induced AEDS and suggested that its routine use might also improve the diagnosis of respiratory allergy to house dust mites.

Cytokine responses to allergens can be detected in cord blood mononuclear cells (CBMC), suggesting allergen priming already in utero. Nilsson et al. (32) found that 53 out of 82 patients with AEDS had significantly lower numbers of IFN γ -producing CBMC after stimulation with various antigens than their non-AEDS counterparts. They found a low number of IL-12-producing CBMC to be associated with IgE sensitization during early childhood and that a reduced number of IFN γ -producing CBMC promotes the development of AEDS during the first 2 years of life (32).

The APT is primarily a tool for investigating the mechanisms of eczema in the skin. It can, however, also reveal sensitization in patients with AD and might identify a subgroup of AD patients (10).

Sensitization to inhalant allergens (e.g., dust, mites, animal dander and pollen) can be detected by SPTs (if the skin is free from eczema) or by measuring specific IgE antibodies.

Contact sensitization to topical medications frequently occurs in AD patients, especially in adults. The possibility of contact allergy needs to be ruled out by patch testing (10, 33).

Treatment

Topical

Management of AD is a clinical challenge. Basic therapy of AD should comprise optimal skin care, addressing the skin barrier defect with regular use of emollients and skin hydration, along with identification and avoidance of specific and nonspecific trigger factors (10). Nonspecific irritants include contactants, such as clothing. Irritating factors also are soaps and hot water during showering or bathing. Mild syndets with an adjusted pH value (acidified to pH 5.5-6.0) should be used for cleansing. There are a number of therapeutic agents for use according to disease severity: basic therapy for solely dry skin, low-to-mid potency topical corticosteroids (TCs) and/or topical calcineurin inhibitors (TCIs) for mild to moderate AD, mid-high potency TCs/TCIs for moderate-to-severe AD, and systemic therapy (e.g. cyclosporine A or phototherapy) for recalcitrant, severe AD. A combination of different topical agents may be indicated. Systemic treatment options are recommended in cases of severe AD.

There is severe dryness of the skin in AD because of an increased transepidermal water loss caused by a dysfunction of the skin barrier (10). The regular use of emollients is important for addressing this problem and, together with skin hydration, it represents the mainstay of the general management of AD. Emollients should be applied continuously, even if no actual inflammatory skin lesions are apparent. Emollients containing polidocanol are effective in reducing pruritic symptoms. Urea is used for intensive hydration of the skin, while salicyl acid can be added to an emollient for the treatment of chronic hyperkeratotic lesions.

Topical corticosteroids (TCs)

Topical corticosteroids have been for several decades the mainstay of AD therapy and other inflammatory disorders. TCs are still important in the treatment of acute flare-ups. Different therapeutic schemes have been established for the topical administration of TCs:

intermittent use may be as effective as an initial therapy with a high potent steroid followed by a time-dependent dose reduction or switch to a lower potent preparation. The choice of an adequate vehicle is important to achieve the optimal therapeutic effect. Treatment with TCs contributes to a reduction of skin colonization with *S. aureus* and may affect a further trigger factor of AD. Only mild-to-moderately potent preparations should be used on genital, facial, or intertriginous skin areas, in short-term application, and only mild-to-moderately potent steroid preparations should be used in children. During acute flares, steroids should be used in combination with emollient skin care to avoid steroid overuse and steroid-related side effects (10).

Topical calcineurin inhibitors

Topical immunomodulators are a relatively new class of medications for the treatment of AD. They are effective for the treatment of AD, but are also effective in a number of other steroid-responsive dermatoses. Tacrolimus (Protopic) ointment is a topical formulation of FK506, and pimecrolimus cream (Elidel[®]) of a new oral ascomycin derivate (34). Tacrolimus and pimecrolimus are selectively inhibitors of the activation of T Cells by inhibiting phosphatase calcineurin. After T lymphocyte activation (after interaction of costimulatory ligands on antigen-presenting cells with T-cell receptor) this increases the levels of free calcium within the cell, which binds to calmodulin and in turn activates calcineurin. Tacrolimus and pimecrolimus inhibit calcineurin and preventing the dephosphorylation activity of phosphatase and the production and release of inflammatory cytokines and T-cell proliferation (34).

It is important in ADS treatment with pimecrolimus and tacrolimus according guidelines and recommendation to include optimal skin care, identification of triggers, treatment of infections and avoidance of allergens (35). FDA raised concerns about potential malignancy risk that can be observed with increased concerns for risk for

malignancy (36). Pimecrolimus and tacrolimus are steroid-free, anti-inflammatory topical medications for the treatment of AD. In the USA and Europe, pimecrolimus cream (1%) and tacrolimus ointment (0.03%) are government-approved for the treatment of AD from the age of 2 years, while tacrolimus ointment 0.1% is only approved in adults. The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with moderate potency. Both agents proved to be effective, with a good safety profile for a treatment period of up to 2 years with pimecrolimus and up to 4 years with tacrolimus (10, 37). Current FDA guidelines recommend that topical pimecrolimus and tacrolimus are indicated for the short-term or intermittent-long-term treatment of AD in patients 2 years of age or older who are unresponsive to or intolerant of other conventional therapies or in whom these therapies are inadvisable because of potential cancer risk (35).

Wet-wrap therapy

A wet layer of cotton dressing in combination with antiseptics or topical steroids (TCs) has been shown to be beneficial in cases of exacerbated AD skin lesions (10, 38).

Topical antimicrobial therapy

Topical antiseptics, such as triclosan or chlorhexidine, offer the advantage of a low sensitizing potential and low resistance rate. They can be used in emollients or a supplement in “wet-wrap dressing” therapy. The combination of a topical antimicrobial agent to a topical steroid preparation has been shown to result in greater clinical improvement over a topical steroid alone (10). A topical antibiotic treatment might be beneficial for the treatment of mild and localized forms of this secondary infection. Topical fusidic acid has proved to be very effective against *S aureus* (application for periods of no longer than about 2 weeks is advisable). Other secondary infections caused by yeasts, dermatophytes, or streptococci have also been implicated as trigger factors in AD and should be treated (10).

Systemic management

Systemic antibiotic treatment is indicated for widespread bacterial secondary infection (primarily *S aureus*). First- or second-generation cephalosporins or semisynthetic penicillins administered for 7-10 days are usually effective. Clindamycin or oral fusidic acid are possible alternatives in cases of penicillin or cephalosporin allergy. Maintenance antibiotic therapy, however, should be avoided since it might result in colonization by methicillin-resistant organisms. Infection with herpes simplex virus (Kaposi's varicelliform eruption) is a severe and life-threatening complication of AD and requires a systemic antiviral treatment with acyclovir or other antiviral agents (e.g., valacyclovir) (10).

Systemic corticosteroids

In cases of acute flare-up, patients may benefit from a short course of systemic therapy with corticosteroids, but long-term use in adults and any use in children should be avoided.

Cyclosporin A

Cyclosporin is immunosuppressive and anti-inflammatory drug. T-cell receptor activation causes release of intracellular calcium that in turn binds to calmodulin and activates calcineurin. Calcineurin complex then dephosphorylates the nuclear factor of activated T-cells (NFATc) which migrate into the nucleus and make complex which is a transcription factor for inflammatory cytokines (e.g. IL-2). Cyclosporin binds to cyclophilin (intracytoplasmic proteins – immunophilin) which blocks the dephosphorylation of NFAT, resulting in a decrease of T-helper cells (CD4) and cytotoxic (CD8) in the epidermis (39). Cyclosporin A (CyA) inhibits calcineurin-dependent pathways, resulting in reduced levels of proinflammatory cytokines, such as IL-2 and IFN-g. CyA is effective in treatment for both adult and childhood AD. Because of the possible side effects, particularly renal toxicity, the use of CyA should be limited to patients

with severe refractory disease. The treatment may be administered in the form of a short- or long-term therapy with high-dose (3-5 mg/kg/d) or low-dose (2.5 mg/kg/d) regimens, depending on the individual patient's medical condition. If after three months of the maximum dose of CyA (5 mg/kg/day), the therapy has failed and should be discontinued (39).

Azathioprine

Azathioprine (Imuran[®]) is a well-known systemic immunosuppressive agent from 1959 that affects purine nucleotide synthesis and is effective in severe recalcitrant AD (10). It has a number of side-effects including myelosuppression, hepatotoxicity, and susceptibility for infection. The recommended dosage of azathioprine for dermatologic indications is 1-3 mg/kg daily but it should be determined based on thiopurine methyltransferase levels (TPMT). Knowing the baseline TPMT activity is clinically useful in the majority of patients who receive azathioprine and to monitoring during the therapy (39). Benefits may not be apparent until 2-3 months after treatment onset.

Antihistamines

The therapeutic value of antihistamines seems to reside principally in their sedative properties, and they are useful as a short-term adjuvant to topical treatment during relapses associated with severe pruritus. The second generation antihistamines, cetirizine hydrochloride, loratadine, fexofenadine hydrochloride have distinct effect because have longer half-lives. Desloratadine has proven effectiveness in controlling pruritus. Nonsedating antihistamines seem to have only very modest value in atopic eczema.

Leukotriene antagonists

Leukotriene antagonists (montelukast and zafirlukast) are useful for the treatment of asthma and allergic rhinitis. In AD therapy is not fully elucidated. Zafirlukast is approved in AD and asthma for adolescents and adults (5). In chronic AD montelukast achieved little

success. Montelukast administered 5 mg daily for four weeks in clinical double-blind study of moderate to severe AD in young patients (6-16 years) showed a significant decrease in disease severity, but in other study with severe AD and different doses (5 mg, 10 mg, 20 mg) there was partial improvement (relieve of pruritus; abatement erythema) in few patients. AD patients failed to show any benefit from leukotriene receptor antagonist therapy (5).

Phototherapy

The following therapy options may be used for AD: broad-band UVB (280-320 nm), narrow-band UVB (311-313 nm), UVA (320-400 nm), UVA1 (340-400 nm), PUVA, and PUVA bath. Combinations of UVB and TCs and UVB with UVA as well as UVA1 medium- and high-dose therapy are useful in AD therapy (40). In the pediatric population, UV therapy should be restricted to children above 12 years of age.

Interferon therapy

Interferons (IFN) are a family of secretory glycoproteins produced by most eukaryotic cells triggered by a variety of viral and non viral inducers. In dermatologic disorders there are three forms of IFN (IFN- α_{2a} ; - α_{2b} and γ) with antiviral, antiproliferative and immunoregulatory clinical effects (34). Evidence of reduced production of IFN- γ in vitro by mononuclear cells of patients with AD, and the suppression of IL-4 mediated IgE stimulation by IFN- γ has prompted evaluation of the use of IFN in AD. In randomised placebo-controlled double blind multicenter trial studies the effects of daily Sc injection (50 $\mu\text{g}/\text{m}^2$) recombinant IFN- γ achieved in 45% - 57% (10-100 $\mu\text{g}/\text{m}^2$) a significant clinical response (34). Therapy with IFN- α has been investigated in patients with AD with varied and contradictory results (34).

Bioengineered immunomodulators

Most of the new approaches aim at inhibiting components of the allergic inflammatory response, including cytokine modulation (e.g., TNF inhibitors), blockade of

inflammatory cell recruitment (chemokine receptor antagonists, CLA inhibitors), and inhibition of T-cell activation (alefacept and efalizumab) (10). For AD treatment bioengineered immunomodulators are in clinical trial phase. Agent that interfere with T-cell activation or T-cell trafficking in the skin (alefacept, efalizumab) are effective in the treatment of psoriasis. They changing the immune profile from Th1 to Th2, or blocking cytokines but this agents are currently in clinical trials for psoriasis and psoriatic arthritis. Infliximab (Remicade[®]) is a chimeric (human-mouse) monoclonal antibody and its target is human TNF- α . Infliximab binds to soluble forms of TNF- α and blocks the interaction of TNF- α with TNF- α receptors. Inliximab is aproved for the treatment of Crohn's disease and rheumatoid arthritis, pioderma gangrenosum and psoriasis (34).

IgE- blocking antibody

IgE-blocking antibody omalizumab (Xolair[®]) is recombinant human monoclonal antibody which is target and specific antihuman IgE drug (binds free serum IgE and avoid the binding to Fc ϵ RI-receptor as well as Fc ϵ RII (CD23) receptor on mast cells, basophyles and antigen presenting cells surface which stops releasing of proinflammatory mediators). Xolair[®] is administrating for adults and children older than 12 years with asthma and AD for three months; than s.c. injections of 0,015 mg/kg IgE and 0,03 mg/kg each two weeks or four weeks. Before the therapy and three months later the down-regulation of IgE receptors is needed. Omalizumab role in dermatology and for AD is probably best directed toward patients with high levels of IgE in whome the IgE is an etiologic factor for their disease (41).

Conclusion

In AD complex and genetically determined aethiopathophysiology there has been major progress in the last decade, but there is no complete cure for AD. Much more clinical

research is needed for therapeutic approach of AD recommended. Patients education programs should be the active part in the management of AD. Management currently focuses on avoidance of triggers, skin hydration and reduction of skin inflammation and AD disease control and prevention of flare.

Summary

We described atopic eczema/dermatitis from the aspects of immunologic background, genetics, skin barrier dysfunction, IgE receptors, and triggers of AD (including allergens, microorganisms, and autoantigens). We have also reviewed diagnostic procedures, treatment modalities with topical treatment (emollients, topical corticosteroids, topical calcineurin inhibitors, wet wrap therapy and topical antimicrobial therapy) as well as systemic management (antimicrobials, systemic corticosteroids, cyclosporine A, azathioprine, antihistamines) and phototherapy. Finally, we have discussed primary and secondary prevention and have emphasized the role of the different cell receptors and their up- and down-regulation in this setting.

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