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Funding Sources: none declared

Conflicts of Interest: none declared

Key words: atopic dermatitis, adults, diagnostic criteria, adult AD, late-onset AD, persistent AD

Word counts: 4593

Figure: 0

Tables: 0

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Abstract

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease which predominantly affects children usually clearing up during or after childhood. However, AD may persist with a chronic recurrent course until adulthood being recalcitrant to any treatment strategy. Moreover, in some patients, AD is not present during childhood but starts later in life (i.e. after 16 years of age) being defined late-onset AD. Even if AD incidence is increasing worldwide with cases in which clinical manifestations first appeared or persisted during adolescence and adulthood raising especially in industrialized countries, studies on adult AD are still scant. Since this subgroup of AD patients often have a nonflexural rash distribution and atypical morphologic variants and validated diagnostic criteria are lacking, there is no clear consensus on the diagnostic work-up that should be performed when evaluating adult patients with AD. In this review, the various aspects of workup in adult patients with AD, such as diagnostic criteria, epidemiology, quality of life and pathogenesis are discussed.

Introduction

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease which predominantly affects children. The disease starts commonly during the first year of life [1] and usually clears up during infancy or childhood [2]. The chronicity and visibility of the disease, together with symptoms such as severe itching, skin damage, soreness and sleep loss may have a profound effect on the quality of life of the patients and their families [3,4].

AD can also be the start of an 'atopic march' which leads to other atopic diseases such as asthma and rhinoconjunctivitis [5].

The pathogenesis of AD remains complex. Gene-environment interactions play a central role [6]. Moreover, there is a variability of systemic and skin immune abnormalities in AD, such as increased serum IgE and allergen sensitization, abnormalities in epidermal barrier [gene mutations encoding proteins such as filaggrin (FLG)], the Th1/Th2 paradigm, and microbe skin colonization [7]. FLG is responsible for the aggregation of keratin filaments, which collapse the granular cells into nuclear squames to form the cornified cell envelope of the stratum corneum (SC) and the skin barrier, protecting the organism against environmental agents and preventing epidermal water loss [8-10]. Skin barrier defects caused by FLG mutations allows the penetration of allergens through the epidermis and their interaction with antigen-presenting cells, leading to the development of atopic disorders, including asthma and rhinitis [11]. Recent studies demonstrated that FLG mutations are strongly associated with increased atopic eczema risk, and probably account for approximately 10% of cases in Europe [12].

AD may persist with a chronic recurrent course until adulthood and this subtype is often very recalcitrant to any treatment strategy [13-14]. Moreover, in some patients, AD is not present during childhood but starts or relapses later in life (i.e. after 16 years of age) [15]. Data about adulthood atopic dermatitis are not very clear. Until the '60s, it was believed that AD was a typical dermatosis

of childhood, with remission in adulthood. From '80s, however, along with an increase in the incidence of the childhood AD, cases in which clinical manifestations persisted or first appeared during adolescence and adulthood have increased especially in industrialized countries, raising the entity of the so-called “adult AD”.

The majority of adult AD patients has only mild disease and is treated by general practitioners, whereas more severe and therapy-resistant patients are frequently referred to dermatologists or allergologists. Apart from the typical flexural dermatitis in adult, this subgroup of AD patients often have a nonflexural rash distribution and atypical morphologic variants, such as nummular or prurigo-like lesions [16].

There is no clear consensus on the diagnostic work-up that should be performed when evaluating adult patients with AD. Therefore, large variations exist in the diagnostic approach. In this review, the various aspects of workup in adult patients with AD, such as diagnostic criteria, epidemiology, quality of life and pathogenesis are discussed.

Epidemiology and *life- course*

The epidemiology of adult AD has been largely neglected. While there have been numerous studies on the prevalence of AD in children and adolescents, there have been only few studies on adulthood AD [17-18]. In addition to the general scarcity of such studies, many of these experiences have been based on hospital outpatient records and the diagnostic criteria used in these studies are different, since they are not unique and uniform in the literature [19]. In Western countries the prevalence of AD in adults was assessed to range from 1% to 3% [3,20]. The lifetime prevalence of AD is considerably lower in the elderly, compared with younger adults [20]. Saeki H et al. evaluated the prevalence of AD in Japanese adults at Kinki University and Asahikawa Medical College [17]. A total of 2137 (1051 men and 1086 women) adult patients were examined. The average age was 40.6 ± 12.0 years (men: 44.7 ± 11.6 and women: 36.7 ± 11.1) ranging from 20 to 69 years. The

prevalence of AD was 6.1% overall, and 10.5%, 7.8%, 3.9% and 2.5%, respectively, for those in their 20s, 30s, 40s and 50s/60s. Discarded the 20s data in order to exclude the influence of the age of adolescence, the overall prevalence would be 4.9%. The prevalence of 30s was significantly higher than that of 40s ($p < 0.01$) [17]. A lower prevalence of AD among Korean adults was reported by Kim MJ et al: 2.6% overall, and 2.4%, 4.5%, 3.2%, 1.2%, and 0.4%, respectively, for those in their 10s/20s, 30s, 40s, 50s, ≥ 60 s [21].

The classical course of childhood eczema shows improvement by adolescence [22]. In a UK study, 74% of the children were clear from symptoms after the age of 16-year. However, a 24-year follow-up study in Swedish children found that 62% of previous inpatients and 40% of outpatients still had dermatitis [13]. In elderly adults with AD, various patterns of lifetime eczema were seen and recurrence of eczema after many years was common. Adult-onset AD is rarer than persistent disease and starts more frequently during the third decade of life [22-24]. In the work by Ellis et al., adult AD has been classified into persistent form (70% of cases), for which the diagnosis is simple, and new form (30% of cases), for which diagnostic criteria are missing [24]. Head-and-neck eczema was a prognostic factor for disease persistence in Swedish adults, whereas Japanese investigators found that high values of serum total immunoglobulin E (IgE) and a long duration of eczema were poor prognostic factors, predicting persisting eczema after 10 years in adults [17,24,25].

Pathogenesis

The SC is the major epidermal component of the so called “epidermal barrier” and is directly involved in several barrier functions. There are several known abnormalities of the SC barrier that may contribute to the disruption of the epidermal barrier resulting in mechanisms that are operative in the pathophysiology of AD [26]. These include defects in FLG, increased serine protease activity, and decreased ceramide fractions and total SC lipid levels [27].

In adults, null mutations in the epidermal barrier protein FLG gene, resident on the epidermal differentiation complex (1q21), were a predisposing factor for persisting eczema of early-onset [28]. The FLG gene is the strongest known genetic risk factor for atopic dermatitis. Around 10% of people from western populations carries mutations in the FLG gene, whereas around 50% of all patients with atopic dermatitis carries such mutations. These mutations give rise to functional impairments in the FLG protein and thereby disrupt the skin barrier. The clinical expression of such impairments is dry skin with fissures and a higher risk of eczema. Not all patients with atopic dermatitis have these mutations and other genetic variants have also been incriminated [29]. In the outer layers of the SC, FLG is degraded into free amino acids, urocanic acid, and pyrrolidine carboxylic acid, which are collectively known as natural moisturizing factors (NMFs). NMFs are formed from the post-translational modification of the c-terminal portion of FLG by caspase 14. NMFs are important to the function of the SC as they provide moisture retention (humectancy), maintain the acidic pH and buffering capacity of the SC, promote proper epidermal maturation and desquamation, and decrease pathogenic bacterial colonization [30].

Serine proteases (SPs) or serine endopeptidases are enzymes that structurally contain the amino acid serine in the active site of the enzyme, and functionally cut peptide bonds in proteins. The function of SPs is often to convert an inactive peptide with a longer chain into an active peptide form that can then induce specific physiological activities [26]. In AD, SP activity is increased and therefore involves adverse effects on some SC barrier functions because it leads to destruction of some proteins that are crucial to SC integrity, interferes with the construction of the intercellular lipid membrane, and increases TH2 inflammation. Increased SP activity decreases SC integrity by accelerating the degradation of corneodesmosomes via the degradation of desmoglein-1 [26,29]. The decreased SC integrity is evidenced by a measurable increase in TEWL and percutaneous absorption [29]. Increased SP activities interfere with the construction of the intercellular lipid membrane by decreasing the total SC lipid content. SC lipid content is decreased secondary to the

increased signaling of the protease activator type 2 receptor and the degradation of two essential lipid processing enzymes beta-glucocerebrosidase and acidic sphingomyelinase [26]. Glycosylceramides, sphingomyelin, and phospholipids are precursor lipids that are stored in lamellar bodies in the granular layer of SC and are converted by specific hydrolytic enzymes to ceramides 1-7, ceramides 2 and 5, and free fatty acids, respectively [26]. In AD, there is reduced total lipid and ceramide content, alterations in subfractions of ceramides, an overall change in lipid composition in the intercellular lipid membrane, and possible altered activity of lipid-modulating enzymes involved in the production and processing of physiological SC lipids that are integral to SC structure and function, especially the permeability barrier [27-30].

Trigger factors

Irritants and inhalant allergens

Irritant factors, such as rough or woolly clothing, may lead to mechanical irritation and worsening of eczema [31]. Also chemical irritants like skin-cleansing agents can exacerbate eczema, especially on the face and hands. Specific challenge test are not available; identification of irritant factors can only be done by elimination.

In daily practice, the relationship between allergen exposure and AD flares is difficult to establish in an individual patient; history is not always helpful. Darsow et al. found that 10–39% of patients reported worsening of eczema after natural exposure to allergens, mostly house dust mite (HDM) [32]. The strongest evidence supporting a role of inhalant allergens in aggravating AD symptoms is based on experimental models. Bronchial inhalation of HDM in sensitized patients with AD and asthma may result in eczematous reactions [33,34]. In addition, epicutaneous application of inhalant allergens on the skin, so called atopy patch test may elicit eczematous reactions after 48–72 h in about 30–50% of sensitized adult AD patients [32]. There is only limited available evidence that allergen-specific therapeutic interventions, such as allergen immunotherapy, are effective in AD.

Food allergens

Classical food allergy has small clinical importance in adults with AD, in contrast to children [35]. However, foods can play a ‘non-classical’ role in eczema. Foods cross-reacting to birch pollen can trigger AD, after oral challenge, in birch-sensitized adults with a negative food history [36]. Most children with AD that react to foods have positive skin prick tests or serum IgE, whereas this may not be true for adults. Finally, certain foods (alcohol, food additives) may cause exacerbations of eczema through non-immune (i.e direct release of histamine) mechanisms and clinical improvement was found in 63% of adult patients after 6 weeks on a low pseudoallergen diet [37].

Allergen-restrictive diets are frequently used by AD patients to improve their eczema. In a recent systemic review of randomized controlled trials to assess the effect of dietary exclusion for improving established AD, Bath-Hextall et al. concluded that there is no evidence of benefit in the use of an elemental or few-foods diet in unselected cases of AD [37]. There also appears to be no benefit of egg- and milk-free diet in unselected adult patients with AD. However, overall interpretation of the studies was difficult because of poor methodological quality and most studies were performed in children [38].

Skin microorganisms

Microorganisms may be a trigger factor for eczematous reactions in sensitized AD patients. In AD patients, *Staphylococcus aureus* (SA) can be cultured from 90% of lesional skin and can also colonize non-lesional skin [39]. The density of SA appeared to be higher in lesional skin than in non-lesional skin and was positively correlated with lesion severity [40]. By contrast, SA can be isolated from the skin of only 5–30% of healthy individuals, mainly from intertriginous areas [6,41]. Even if there are no clinical signs of infection, SA may play a role in promoting skin inflammation in AD by secreting toxins with superantigenic properties resulting in marked activation of T cells and other immune cells [42].

Malassezia (M) yeast colonization is higher in adults, as compared with children with AD. The prevalence of serum IgE antibodies to the species *M. furfur* is also much greater in adult patients [43]. IgE antibodies against M species were found mostly among adult patients with elevated total IgE levels [22]. Clinically, M sensitization may be suspected in patients with eczema localizations on forehead, eyelids and neck (head and neck dermatitis). These patients may be refractory to conventional treatment such as topical steroids [44]. In contrast to SA, there is no convincing evidence that the skin of patients with AD is more heavily colonized when compared with healthy subjects [3].

Contact allergens

Impaired skin barrier function and hyper-reactivity to irritant stimuli can enhance delayed type contact allergy in AD patients. AD is a risk factor for allergic contact sensitization, according to a recent Scandinavian adult population study [45]. Contact allergy increases with age in atopics: nickel, constituents of cosmetics and topical treatments are relevant contact allergens [46]. Because AD patients tend to use topical steroids for a long period of time, they may develop allergic contact dermatitis to corticosteroids. In a recent study, 3547 patients were patch tested with detectors of corticosteroids contact allergy (tixocortol-21-pivalate, budesonide and hydrocortisone-17-butyrate). In total, 72 individuals (2%) of the study population had a steroid allergy: 0.8% had a tixocortol-21-pivalate allergy, 1% a budesonide allergy, and 1% a hydrocortisone-17-butyrate allergy. Tixocortol-21-pivalate and budesonide allergy were associated with AD in crude analyses, but only tixocortol-21-pivalate allergy and AD remained associated in adjusted analyses. Leg dermatitis was uniquely associated with tixocortol-21-pivalate allergy [47]. Chronic dermatoses (AD and leg dermatitis) were identified as risk factors for group A corticosteroid allergy, probably because of more pronounced exposure to group A steroids resulting from ease of access that is exploited by patients with a chronic dermatosis [47].

Diagnosis

There are no biomarkers available for the diagnosis AD as it primarily depends on the clinical manifestations of the disease and the family history of the patient concerning atopic diseases. The main symptom of AD is intense itch. The type and location of skin lesions vary with patient age and the course and duration of the disease. Infantile AD commonly presents on the cheeks, whereas childhood AD occurs in flexural areas, and adult AD is often reflected as hand dermatitis [48]. Less frequent manifestations of AD can be divided into localized (site specific) and disseminated (morphological) variants [49]. The localized variants of AD are eyelid eczema; infraauricular, retroauricular, or infranasal fissuring; fingertip eczema; atopic feet; cheilitis; nipple eczema; and genital dermatitis. The morphologic variants of dermatitis are follicular, papular-lichenoid, prurigo-like, nummular pattern and erythroderma [16]. The clinical appearance of AD in adults is similar to that in later childhood, with lichenification, especially of the antecubital flexures, eyelids, perioral region and popliteal flexures. The involvement of forehead, cheeks and anterolateral region of neck, however, is very common in adults [48].

Several sets of diagnostic criteria have been developed in an attempt to better define the disease [50,51]. Diagnostic criteria are based on an objective evaluation of skin lesions by a clinician and a subjective evaluation of the symptoms by the patient. The diagnostic criteria presented by Hanifin and Rajka in 1980 are still the most commonly used diagnostic criteria for AD. A refinement of these criteria was introduced in 1997 by Williams et al. [51]. These so-called UK diagnostic criteria for AD consist of one mandatory and five major criteria, and are more manageable for daily practice. The limit of these criteria is that they have been developed to identify AD in children and then adapted to adults; this could translate into a reduction of specificity and sensitivity.

Some authors have tried to define specific criteria for AD of the adult. Garmhausen et al. show that the natural course of AD can be divided into 5 subgroups that display different clinical features

[15]. This heterogeneity might be, amongst other factors, the reason for the high number of variations of the results of different genetic, clinical and research studies on adult AD. Moreover, the Authors emphasize the need for careful stratification of patients with AD in the clinical practice as a first approach to individualized therapy and more careful definition of AD subtypes in clinical and research studies to achieve better comparable results [15].

Ozkaya reported that patients with adult-onset AD had a mean number of 7 minor criteria according to Hanifin and Rajka (range: 3-13) [52]. The severity of AD correlated well with the frequency of minor criteria: the less the minor criteria the milder the disease [52]. Similarly, Loden et al. showed a positive relationship between the number of minor criteria and the severity of dryness [53]. An interesting finding of the study conducted by Ozkaya was that UK criteria did not cover the same patients as the criteria of Hanifin and Rajka. Apparently, there is no problem in detecting early-onset according to these criteria. However, approximately in one fourth of patients the diagnosis of adult-onset AD was not possible according to UK criteria in its current form [52].

Wanitphakdeedecha et al. proposed that the most useful diagnostic criteria for Thai people older than 13 years consisted of a history of itchy rash, a history of flexural dermatitis, chronicity for more than 6 months, visible xerosis, periorbital dermatitis, and follicular keratosis [54].

Skin biopsy specimens or other tests such as serum IgE, patch testing, and/or genetic testing may be helpful to rule out other or associated skin. Unfortunately, so far there are no specific laboratory markers to evaluate AD severity, but high IgE serum levels and eosinophil blood count are frequently found in AD patients. Moreover, all patients with AD should undergo a patch testing: the identification of contact allergens is very important because it may influence the clinical course of AD, the patient's occupational choices, and the development of hand dermatitis among those who work in certain occupations. Indeed, all the patients with chronic relapsing or persistent dermatitis, especially in older age, with lack of expected improvement in a corticosteroid-responsive

dermatosis in spite of adequate treatment or with aggravation of a dermatosis after topical corticosteroid treatment should be patch tested.

Differential diagnosis

The differential diagnosis of AD is very broad and includes other chronic inflammatory skin diseases, infections, malignancies, metabolic and genetic disorders, and autoimmune disorders. Other eczematous diseases, such as contact dermatitis (allergic and irritant) and seborrhoeic dermatitis may mimic AD: history is often helpful to discriminate. Additional patch testing may be relevant in selected cases. Sometimes, it is difficult to discriminate AD from psoriasis. Other possible differential diagnoses are scabies, dermatomycosis and cutaneous T cell lymphoma [3]. In a case-control study, Arellano et al. found that AD was associated with an increased risk of lymphoma (OR, 1.83.) Severe AD further increased the risk of lymphoma (OR, 3.72) [55].

Quality of life

Quality of life is compromised in adults with AD, both related to disease severity and to emotional components [22]. Factors such as severe itching, scratching, sleep loss and social embarrassment may lead to social isolation, discomfort at school and/or work ,and financial problems in individual patients. Among dermatologic adult outpatients evaluated by Dermatology Life Quality Index (DLQI), AD patients were the worse scoring group [56]. Besides, AD may be responsible for indirect costs such as purchase of special household items and days lost from work [57]. Concerning the degree of handicap in relation to the choice of educations and occupation, 38% of AD patients had abstained from a specific education or job due to AD, and even mild-to-moderate disease causes handicap, as seen from increased sick leaves and early retirement pensions [22,58]. Indeed, AD is a common cause of occupational dermatitis and doubles the risk of developing irritant dermatitis, particularly in occupations involving wet work [59]. In atopic adults, occupational contact dermatitis can precipitate generalized eczema with an AD pattern [60].

Eczema can persist even after removal from a high-risk occupation. Thus, pre-employment counseling of adolescents and adults with atopic eczema is important [59,60]. Finally, a decrease in sexual desire due to AD was noted in 57.5% of the patients, while 36.5% of partners reported that eczema had an impact on their sex life [58].

Treatment

The treatment of AD aims to minimize the number of exacerbations of the disease, so-called flares, and to reduce the duration and degree of the flare, if flare occurs [1,2]. The treatment of adult patient is generally more simple, by the number of drugs to which they can appeal. In 2012, Ring et al. have proposed updated guidelines for the treatment of AD (not only adult AD) [61].

Topical treatment

The use of topical steroids for acute flares, together with maintenance topical calcineurin inhibitors, is recommended [22]. Topical tacrolimus is more effective than pimecrolimus in adults with moderate-to-severe AD, but both agents have a similar safety profile and can be applied on areas with sensitive, thin skin (face, eyelids) [62]. In adults with AD, tacrolimus ointment was effective and well tolerated, for up to 2 and 4 years [63]. Adults with refractory AD greatly benefit from 7 days of wet-wrap dressings with diluted steroids [61]. The use of emollients in the management of atopic dermatitis is pivotal. They should be applied several times a day, and a systematic use has been shown to reduce the need for corticosteroid creams [59]. The main reason for intensive use of an emollient is its ability to increase the hydration of the epidermis, mainly by reducing the evaporation, as it acts as an occlusive layer on the top of the skin [64]. The choice of emollient depends on the individual patient. It is generally recommended that a thick (with a high fat content) cream or ointment is used for the driest skin, whereas creams and lotions with a higher water content are used only for very mild eczema. Such creams must be applied several times a day because of their rapid absorption into the skin. It is important to recommend an emollient without

perfume or other potential allergens as they may provoke secondary contact allergic sensitization [59].

Phototherapy

As most patients affected by atopic dermatitis improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AD. Present UV sources include equipments able to emit selective spectres of radiations:

- UVA + UVB (approx. 280–400 nm).
- Broadband ultraviolet B (BB-UVB = approx.280–320 nm).
- Narrow-band UVB (nbUVB = peak: 311–313 nm).
- UVA1 (340–400 nm)

As a rule, phototherapy is not indicated in the acute stage of AD (except UVA1, which is also effective in managing AD flares), but is more apt to treat chronic, pruritic, lichenified forms and should not be prescribed in those patients who experience a worsening of their dermatosis during sun exposure. In practice, the choice of a certain UV treatment is limited by the availability of the phototherapy equipments: e.g. UVA1 devices are expensive to buy and to maintain [61].

Narrowband UVB light is particularly suitable for treating adults with recalcitrant eczema. Broadband UVA light and a combination of UVA light and the a photosensitizing drug (psoralene) (PUVA) can also be used to treat severe recalcitrant eczema. Difficult-to-treat AD often clears with 1-2 months of phototherapy three to five times a week, preferably combined with topical corticosteroids. Nevertheless, as all UV treatments pose a long-term risk for development of skin cancer and premature aging of the skin, it should be prescribed with caution [61].

Systemic Treatments

Sedating antihistamines can reduce itch during relapses, but they affect driving skills, and should not be combined with alcohol, or certain antidepressants [31]. Antihistamines have been used for decades, in an attempt to relieve pruritus in patients with AE. However, only a few randomized controlled trials have been conducted and they have in the majority shown only a weak or no effect in decreasing pruritus. The first generation of sedative antihistamines, such as hydroxyzine, clemastine fumarate and dimetinden maleate, may allow a better sleep pattern in acute situations with exacerbations of eczema (evidence level D) [61]. Concerning the newer non-sedating antihistamines, single studies using loratadine, ceterizine or fexofenadine demonstrated no or only a weak relief of pruritus in AD [61].

Short-term tapered treatment with oral corticosteroids (20–40 mg prednisolone) is recommended for acute flares of severe, widespread atopic dermatitis, also in combination with topical corticosteroids [22]. Older patients should be closely monitored for increased blood glucose, increased blood pressure and ocular side-effects.

For widespread bacterial skin infections, erythromycin, clarithromycin, semisynthetic penicillins or cephalosporins, used for 7–10 days, are effective, but recolonization occurs soon after treatment [65]. SA is universally resistant to penicillin in adults [58]. In adults with IgE hypersensitivity to skin yeasts and positive cultures, oral azoles improve eczema, but long-term studies are lacking [66].

Instead, tapering should be done while introducing a second immunosuppressant drug, for example, azathioprine, methotrexate, or cyclosporine A, for very severe, chronic, relapsing AD. Azathioprine is used for systemic treatment of AD when there are no other alternatives. It works well with good response, but it is not always well tolerated [67]. Leukopenia and liver function abnormalities have been reported. Treatment dose of 1.5-2.5 mg/kg/daily is used [68]. The enzyme thiopurine

methyltransferase plays an important role in metabolizing the drug and deficiency of this enzyme has been associated with a high risk of myelosuppression [68]. A study by Schram *et al.* compared the efficacy and the safety of MTX and azathioprine in adults with severe AD. The drugs were equally effective, achieved significant improvement and were safe for the study-period of 12 weeks [69]. It was reported in two different double-blind placebo-controlled randomized controlled trials (RCTs) that oral cyclosporine was superior to placebo [70,71]. The efficacy of cyclosporine at a dose of 3-5 mg/kg/daily was demonstrated both in adults and children [71] .

Other Medications

A recent, placebo-controlled study in adults with AD sensitized to dust mite, demonstrated improvement in severity scoring, after 4 months of specific immunotherapy with dust mite, especially in patients with severe AD [72].

Interferon alpha and interferon gamma and infliximab have been tried in severe AD, but there are too few, well-carried out, studies to justify their use in adults [71].

Omalizumab is a humanized monoclonal anti-IgE antibody that binds to the IgE molecule at the high affinity FcεRI receptor binding site. The drug has been approved by the Food and Drug Administration for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma. Since AD shares a common pathologic mechanism with asthma, that is IgE reactivation, omalizumab has been tested as a systemic therapy for recalcitrant AD associated with elevated IgE levels [73]. Kim et al. [74] reported a study of 10 patients with AD (aged 19–35 years) who received anti-IgE treatment. All patients, regardless of IgE value, were treated with a fixed schedule of eight cycles of omalizumab 300 mg administered subcutaneously at intervals of 2 weeks. Clinical improvement became evident after approximately 2 months of treatment. Once a clinical improvement occurred, none of the patients experienced worsening of their eczema

symptoms again while on omalizumab, and the improvement was maintained until the assessment 4 months after the end of treatment [73].

Dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin- 13, has shown efficacy in patients with asthma and elevated eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)–mediated inflammation could help in the treatment of related diseases, including AD. Patients treated with dupilumab had marked and rapid improvement in all the evaluated measures of disease activity. Side-effect profiles were not dose-limiting [75].

Conclusion

AD incidence is constantly increasing with adult and persistent AD enhancing especially in industrialized countries. Adult AD frequently shows atypical clinical and morphological features with related diagnostic challenges also because validated diagnostic criteria are not available. Without any doubt further studies and more efforts are needed to deepening the knowledge regarding adult AD highlighting also eventual pathogenesis, comorbidities, treatments, etc, peculiarities which may differ from childhood AD.

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