Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Case Report

Successful Control of Some Challenging Cases in Late Adult and Elderly Onset Atopic Dermatitis with Dupilumab Injection in Kuwaiti Patients: A Prospective Pilot Study

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Citation: Almasry I, et al. Successful Control of Some Challenging Cases in Late Adult and Elderly Onset Atopic Dermatitis with Dupilumab Injection in Kuwaiti Patients: A Prospective Pilot Study. J Dermatol Res. 2024;5(1):1-10.

https://doi.org/10.46889/JDR.2024.5104

Received Date: 01-11-2023

Accepted Date: 15-01-2024

Published Date: 22-01-2024

Abstract

Atopic Dermatitis is severely itchy skin disease with chronic prolonged course and relapsing flares, which was considered mainly infantile or childhood in onset for a long time. Atopic Dermatitis is not any more a pediatric dermatosis, an emerging new entity in adult and elderly patients became more and more identified. An elderly onset of Atopic Dermatitis is mainly due to aging process. There are various causes that reduce skin function, especially senile xerosis of skin in these age group. Dryness itself makes skin as weak as a protective barrier in elderly, in addition to pathophysiological changes in aging human skin. All previous factors might trigger Atopic Dermatitis pictures over elderly patient. Atopic Dermatitis in elderly might does not look so bad as morphological reflection on skin, but intolerable pruritus' accompanied this skin condition is more concerned. Dupilumab as well-known safe and effective controlling therapy for atopic dermatitis, given a light at end of tunnel specially for severe pruritus' which affect badly life quality in these poor patients. This article represents a close review of etiopathogenesis of late adult and elderly onset atopic dermatitis. Also, we represent 10 cases of confirmed late adult and elderly Atopic Dermatitis who have a proper control on Dupilumab injection safely without any drawbacks on patients.

Keywords: Atopic Dermatitis; Dupilumab Injection; Diabetes Mellitus; Hypertension

Abbreviations

Pt: Patient; Y: Year; F: Female; M: Male; DM: Diabetes Mellitus; HTN: Hypertension

Introduction

There are variable skin manifestations are concerned in elderly populations due to multiple morbidities in this particular age group. Elderly onset Atopic Dermatitis is one of skin manifestations which underestimated diagnosis in elderly. Atopic Dermatitis 98 (AD) is severely itchy skin disease with chronic prolonged course and relapsing flares, which had been considered as a 'children disease 'for a long time [1]. Nowadays Atopic Dermatitis is not any more a pediatric dermatosis only, as an emerging new entity in adult and elderly patients became more and more identified [2-5]. The aging process causes various reduced skin function, which leads to atypical clinical features of AD in elderly [3]. According to the definition by the World Health Organization (WHO), elderly age is considered in those aged over 60 years [4]. Atopic Dermatitis in adulthood and elderly has shown an increased rate as high as an almost three folds between

2012 and 2013 [5,6]. The reported prevalence of AD in adult patients 1- 3% and in elderly 2.6% (age 60 years and over) in Japan [2,6].

Pathophysiological causes of Elderly (senile) AD. The pathogenesis of Atopic Dermatitis is multifactorial, involving genetic, immunologic and environmental factors that disrupt the skin barrier [7]. In the following, some of these factors that raised as initiations or triggers of AD in elderly age will be reviewed in brief, special focus on skin aging.

Human Skin Aging

Our skin is a mirror to our health with a natural cover protector function, in addition to other many physiological functions. The skin is the natural source of vitamin D (vit.D), which is produced locally from 7-dehydrocholesterol in photoreaction induced by Ultraviolet B (UVB) radiation, which found lower in representative residents for older Europeans aged 75-76 years [8]. The role of vitamin D in pathogenesis of allergic skin diseases and AD has been reported through its role by interfering in the regulation of both innate and adaptive immune systems [9]. Accordingly low vit.D in elderly age group and its postulated role in AD might be considered one of Hypothetical contributing theories in AD pathogenesis [8,9]. At the cellular level the aging process was linked to shortening of telomeres, first discovered in1986 [10]. Skin is one of visible organs that showing clearly human aging as it thins, dries and becomes unevenly pigmented [11]. Chronic dryness and itching are particularly prevalent in one study of healthy Japanese over 60 years of age, 95% suffered dry skin at least part of the year [11]. Skin functions as protector from external stimuli and to maintained hydration are decreased more and more with skin aging [12].

Traceable Physiological Changes of Human Skin Aging

Skin aging is accompanied by degradation of collagen and elastic fibers in the dermis, thinning of the epidermis and impaired fibroblast function [13]. These changes have been shown to impair cutaneous integrity, wound healing and sensory and immune function [14]. The immune response of aged skin is generally diminished, numbers of Langerhans cells in the epidermis decrease by about 50% between the age of 25 and the age of 70 [12]. The total number of circulating lymphocytes decreases, as does the number of T-cells and B-cells [13]. In the contrary the Levels of circulating autoantibodies increase with age; this occurs in parallel with a decrease in useful antibodies as the aged individual's existing immunity to specific allergens attenuated [14,15]. A recent experimental study has shown that a different function of lymphatic system away from fluid transport and homeostasis might play a critical role in antigen delivery and immune homeostasis [16]. In other side it is well known that dysfunctional lymphatic system is associated with chronic low-grade inflammation of peripheral tissues, poor immune responses and recurrent infections, which are also hallmarks of aging pathology [17,18]. Migration of immune cells through lymphatic channels to site of tissues inflammation is one of important function of competent lymphatic system, dependent on chemokines and adhesion molecules expressed on Lymphatic Endothelial Cells (LECs) [19]. A marked decrease in trafficking of Dendritic Cells (DCs) through lymphatic channels from the periphery to the draining LN with aging was reported, but different DCs subsets play distinct roles in the immune response mediate immune stimulation or immunotolerance [16,19]. More pointed to lymphatic role in immune response, that most inflammatory cells in skin were clustered around lymphatic vessels with upregulation of Intercellular Adhesion Molecules (ICAM-1) and P-selectin and downregulation of Chemokine Ligand 21 (CCL21) over Lymphatic Endothelial Cells (LECs) in aging skin [16]. It had been reported that some adhesions molecules are over expressed in atopic dermatitis, even in non-lesional skin, mainly E-selectin (ELAM-l), L-selectin (LECAM-l) and also P-selectin (CD62), Intercellular Adhesion and Molecule-1 (ICAM-l) [20].

Etiopathogenesis of Atopic Dermatitis in Elderly (Postulated Theory)

There is impairment of skin as physical, physiological, environmental with skin aging, which alter skin immune barrier due to improper enzymatic process specially at level of stratum corneum layer, resulting in increased water loss and more skin dryness [21]. External factors like pro-oxidative air pollutants oxides, Volatile Organic Compounds (VOCs) and O3 have a well-established role in aging skin process and prolonged exposure to their high levels can induce alterations in skin homeostasis and result in inflammatory skin conditions such as AD and eczema [22]. In elderly skin, there is reductions in water and lipid contents, which are natural moisturizing, in addition to insufficient ceramide contents due to decreases degradation of corn desmosome [23,24]. Lack of skin moisturization leads to skin dryness and impaired physical barrier which gives easy entry of different allergens, irritants and pathogens [25]. In elderly an altered immune response is well settled inform of relatively reduction in the level of suppressor T-cells, while memory T cells are increased, although the total number of T cell decreased as well as a there

is a reduced number of naïve T-cells [26-28]. This alteration might be supporting AD like in elderly, which mimic dermatitis found in the primary T-cell immunodeficiency disorders [29]. The aged epidermis increases susceptibility to irritant contact dermatitis and impaired permeability to the drug, suggesting alterations of the skin barrier and barrier function is diminished [30]. A high protease activity and a decreased production of Natural Moisturizing Factor (NMF informed from the proteolysis of FLG all are added contributing factors in etiopathogenesis of Atopic Dermatitis in Elderly [30].

Skin Morphology and Diagnostic Features of Atopic Dermatitis in the Elderly

Atopic Dermatitis is seen in approximately 10% to 30% of children and 2% to 10% of adults in developed countries, a new classification of AD into three subsets based on the age of onset [31].

1. Early-onset Atopic Dermatitis (birth to 2 years old): most common type of atopic dermatitis, with approximately 60% of cases starting by age 1, Sixty percent of cases resolve by 12 years old
2. Late-onset atopic dermatitis: symptoms begin after the onset of puberty
3. Senile onset atopic dermatitis: an unusual subset with onset in patients older than 60 years old. This updated classification for AD is more presentable to newly identified types beyond the previous known childhood and adulthood AD subtypes

Elderly AD might have three patterns, as started either in childhood with recurrent history of classic AD, recurrent or continuity of AD in adulthood, or late senile onset [32]. Skin morphology in elderly AD similar to those in adult AD, such as chronic eczematous lesions on the face and neck, lichenfication on the trunk and extremities and infra-orbital, Dennie-Morgan folds may be shown in some patients (Fig. 1). Hertoghe's sign are applicable in senile AD, in addition to reverse sign of lichenfication around the unaffected folds of elbows and knees is common (Fig. 1) [33]. Other clinical stigma of AD facial erythema and pallor, dirty neck, follicular lichenified papules "portrait" type extends to seborrheic areas morphology similar to pittosporum folliculitis (upper chest, back) (Fig. 1) [33,34]. Elderly patients with pruritic skin complain for more than 2months with excluding any other differential dermatoses causing chronic pruritus whatever in primary skin disorders or internal systemic morbidities, also exclude contact dermatitis or autosensitizations, an elderly AD can be settled in addition to other morphological characteristic of AD [2,33,34].

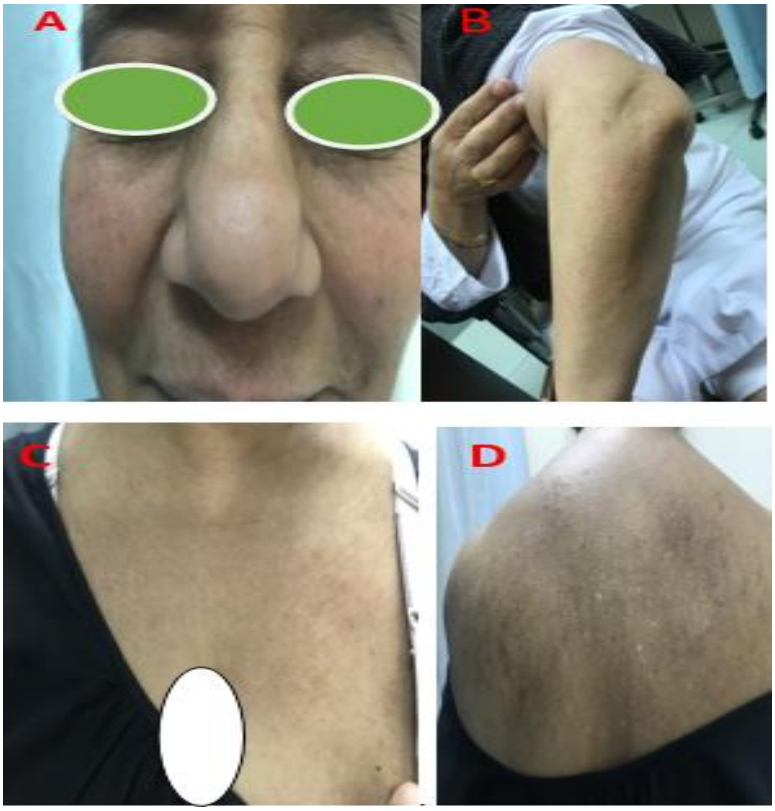

Figure 1: An elderly AD female patient, 63 years with: A): Dennie-Morgan fold fold both eyes; B): Lichenification around the unaffected folds of elbow (The reverse lichenification sign); C&D): "portrait" type, extends to seborrheic areas (anterior chest and upper back) (portrait sign).

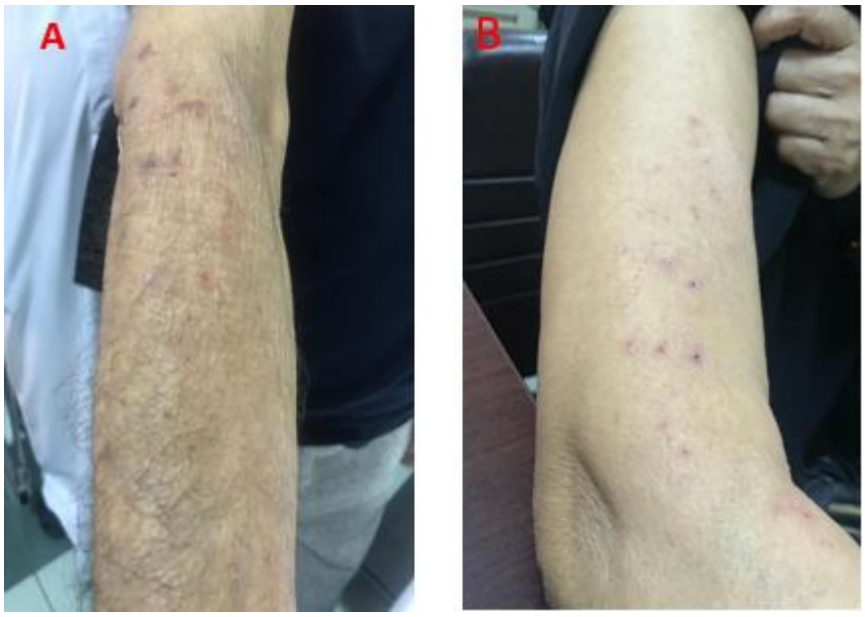

Figure 2: A: Male patient 84 year with lichenification around the unaffected folds of elbow (The reverse lichenification sign); B: Female patient 62 years, senile Atopic Dermatitis (*Prurigo nodularis* type).

Material and Methods

Our study done at a single tertiary care center. In the start of it, there were 11 Kuwaiti patients who are regularly following up in subspecialty Atopic Dermatitis clinic. Only 10 participants patients have continued the study, one patient excluded after first loading dose of Dupilumab injection due to sever drug hypersensitivity reaction.

All participants had given an 'informed consent' for sharing in the study and all obtained information and taken photos are maintained with full confidentiality. The inclusion criteria for studied patients were as the following:

1. Patients given consent
2. Confirmed diagnostic criteria of AD in this age group according to published studies published studies [2,33,34]
3. Age above 50 years
4. Both sexes were involved
5. Hold on previous systemic treatments for 3 months (Omalizumab, steroids)
6. Patients who regularly adherent to Dupilumab injection for at least 24 weeks

Exclusion Criteria

1. Patients refused to share in the study
2. Patients were not adherent to regular dosage schedule for at least 24 weeks
3. Patients below 50 years
4. Patients not fulfil diagnostic criteria for AD
5. Active malignancy or history of malignancy within 5 years before baseline
6. Severe renal or liver conditions
7. Active chronic or acute infection skin or systemic (active T.B or severe herpetic infection)
8. Known or suspected immunodeficiency
9. Patients who known allergy to Dupilumab before or develop it during the study
10. Exclude other dermatological or medical morbidities for chronic itching

All patients diagnosed with Atopic Dermatitis after at least six months of symptom assessment and all other conditions had been excluded like cutaneous T-cell lymphoma, allergic contact dermatitis, bullous pemphigoid and dermatitis herpetiform. Exclusions of other dermatologic condition depend on taking thorough history, proper skin examination and blood tests and skin biopsy for routine H&E examination with immunostaining if needed like in suspected bullous pemphigoid or dermatitis

herpetiform. All patient demographic data were collected, age, sex, duration and onset of AD as well previous treatment taken. The SCORAD (SCORing Atopic Dermatitis) was used as severity assessment and DLQI for assessment of AD burden on patients" life. Diagnostic criteria in participant patients are same as in young age group which are: chronic eczematous lesions on the face and neck, lichenfication on the trunk and extremities and infra-orbital Dennie-Morgan folds in addition chronic pruritus for 6 months or more. Subtypes of different clinical phenotypes types of AD were included such as prurigo nodularis, nummular eczema or generalized eczema [35]. Regular follow up for studied patients for 24 weeks with complete adherent to dupilumab injection recording SCORAD and DLQI.

Dupilumab injection was given as same dosage schedule for adult patient as 600 mg subcutaneous loading dose at W0 then dupilumab 300 mg subcutaneous injection ever two weeks (FDA approved 2017) [36].

Results

The participant patients are 10 ,5 females and 5 males (One female patient had been excluded at start of the study). The mean age is for the 10 patients 71 year ± 8.37. Diagnosis of AD in the studied patients was done according to the presentable skin lesions and prolonged pruritus, the average duration of AD is 4.6 year, all demographic information for 10 patients in Table 1. All other medical causes of chronic pruritus were excluded through doing basic blood chemistry for renal and liver functions, CBC and total serum IgE as well immunological lab work up for immune bullous diseases. Skin biopsies were done for point 8 and 10 as bullous pemphigoid and dermatitis herpetiformis were suspected respectively for direct immunofluorescent study which become negative and histopathology was consistent with dermatitis. Evaluation of AD improvement in each patient was assessed by using SCORAD at W0 of Dupilumab injection and then biweekly at every dupilumab injection until W16, as showed in Table 2, Fig. 4. The DLQI was measured at same manner W0 till W16.All 10 patients have shown initial and sustained improvement both in skin morphology and pruritus which was reflected on DLQI improvement as showed in Table 2, Fig. 5. Dupilumab injection has been continued for all patient beyond W16 with continuous and maintained improvement for 2- 3years until now without any adverse effect in the ten patients and there is steady and sustained reduction in SCORAD and DLQI during the treatment Fig. 4,5.

Pt.No.	Age	sex	Duration	Onset	Morphology.AD	Comorbidities
Pt.1	56	M	5y	Childhood	Lichenified dermatitis	Cholinergic urticaria
Pt.2	78	M	13y	Senile	Lichenified dermatitis	Hyperlipidemia, HTN
Pt.3	62	F	5 y	Senile	Prurigo nodularis	DM
Pt.4	84	F	4Y	Senile	Lichenified dermatitis	Interstitial lung disease DM, autoimmune thyroiditis, cholinergic urticaria
Pt.5	67	M	3Y	Late adult	Disseminated dermatitis	DM, HTN
Pt.6	81	F	4y	Senile	Prurigo nodularis	DM, HTN
Pt.7	63	F	4y	Senile	Lichenified dermatitis	DM, Hyperlipemia
Pt.8	85	M	5y	Senile	Disseminated dermatitis	Alzheimer's disease, DM, HNT
Pt.9	64	M,	6Y	Senile	Disseminated dermatitis	HTN
Pt.10	83	F	3Y	Senile	Disseminated dermatitis	DM, HTN

Table 1: Demographic data and AD. morphology of studied patients.

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7	Pt.8	Pt.9	Pt.10
SCORAD										
W0	24.16	42.5	35.3	31.2	60.2	70.5	45.4	50.2	40.2	29.5
W2	16.9(30%)	36.1(15%)	30.00(15%)	24.9(20%)	45.15(25%)	49.35(30%)	34.95(23%)	45.18(10%)	28.14(30%)	22.12(25%)
W4	13.52(50%)	28.98(35%)	25.5(30%)	22.4(30%)	40.6(35%)	44.41(40%)	30.75(35%)	40.66(20%)	25.32(40%)	18.80(40%)
W8	11.49(75%)	24.63(45%)	19.2(55%)	20.16(40%)	36.5(50%)	39.08(52%)	27.67(45%)	34.75(35%)	21.55(55%)	16.9(50%)
W16	10.11(77%)	19.70(65%)	16.3(70%)	15.12(65%)	32.9(60%)	35.17(62%)	24.97(55%)	29.55(50%)	20.47(60%)	15.21(60%)
DLQI										
W0	23	18	15	26	14	12	25	27	28	21
W2	16(30%)	13(25%)	11(30%)	22(15%)	11(20%)	8(30%)	18(30%)	19(30%)	21(25%)	17(20%)
W4	14(40%)	11(35%)	10(40%)	19(30%)	9(35%)	7(40%)	14(50%)	17(40%)	19(40%)	14(35%)
W8	11(60%)	10(40%)	9(45%)	13(60%)	7(45%)	6(55%)	12(65%)	15(50%)	17(50%)	13(45%)
W16	10(65%)	9(55%)	7(60%)	10(70%)	5(55%)	5(65%)	10(75%)	12(70%)	14(65%)	12(55%)

Table 2: Intial and Sustained Improvement in SCORAD and DLQI in Studied Patients under Treatment with DUPIXENT Injections (WO-W16) (SCORAD: Severity Scoring of Atopic Dermatitis, DLQI: Dermatology Life Quality Index.).

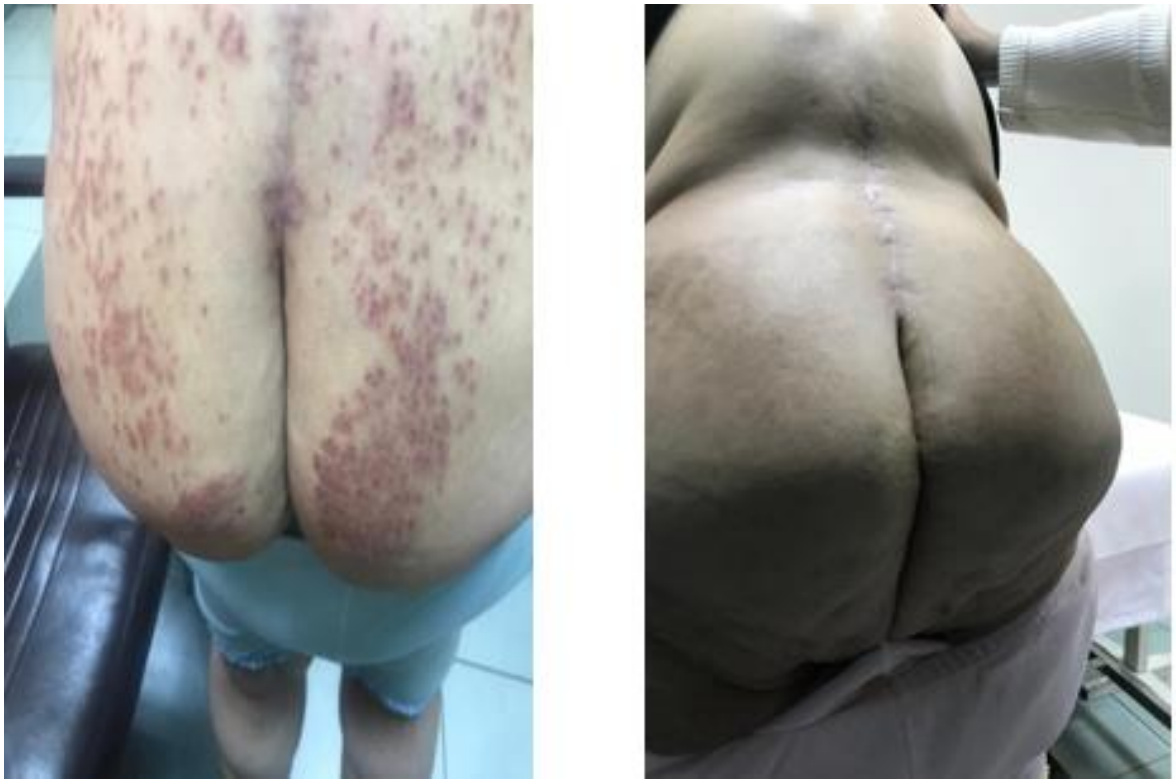

Figure 3: Female patient 83 years, senile AD with improvement of skin lesions after Dupilumab injections (Pt.10).

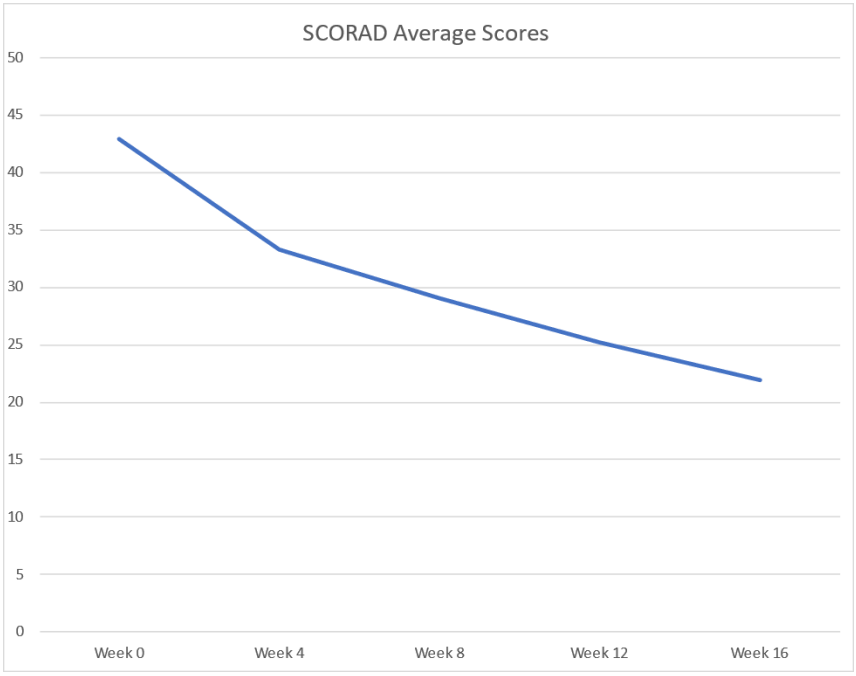

Figure 4: Average SCORAD scores for 10 included patients measured on weeks (0,4,8,12,16) on Dupilumab therapy.

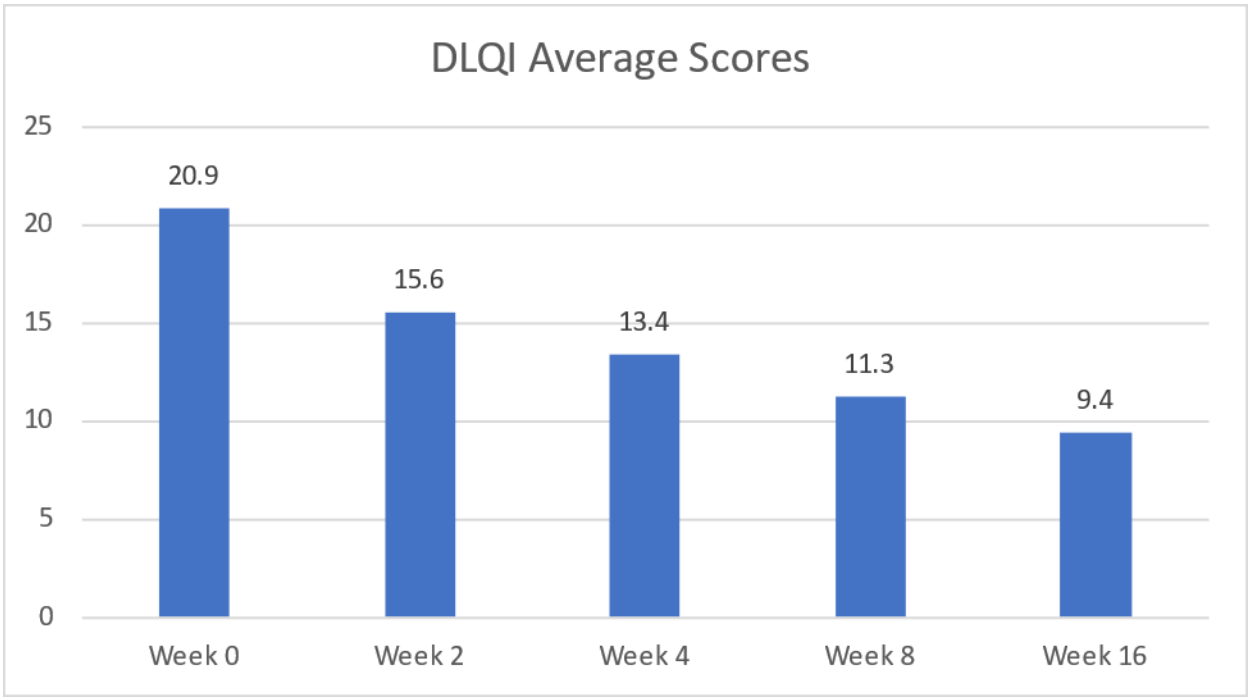

Figure 5: Average DLQI for 10 included patients measured on weeks (0,4,8,12,16) on Dupilumab therapy.

Discussion

Atopic Dermatitis in older adult and elderly patients became more and more reported in several publications specially in industrialized countries associated with an aging society [30,32-34]. Diagnosis of elderly AD could be represented with three patterns according to the onset, with variable morphological phenotypes [35]. Etiopathogenesis of elderly AD resumed to many physiological and immunological changes happening in skin aging [12,13,20]. Both extrinsic and intrinsic forms of AD exist in the elderly, the major environmental allergens in the extrinsic form are house dust mite, followed by pollens and foods [30]. There are many age-related changes overlap etiopathogenesis of elderly AD, mainly skin barrier impairment and immune cell's role might be considered the key hallmarks observed in elderly AD [30]. Notably a decline in skin barrier function, dysregulation

of the innate immune system and skewing of adaptive immunity to a type-2 T helper cell response, in addition to increased Staphylococcus aureus infection [12,13, 30]. Management of AD in elderly patients is challenging both in diagnosis and treatment, two of our participant patients (Pt 1 and 4) patients had been diagnosed as urticaria by other dermatologists because of chronic itching, although they never experienced any urticarial wheals, proper taking history and examination of them had revealed that they have concomitant cholinergic urticaria and elderly AD according to AD diagnostic criteria in these age group [33,34]. These two patients had been under treatment of Omalizumab for years with very poor response. Both cholinergic urticaria and AD of these two patients have been controlled after shifted to Dupilumab injection during the study. Dupilumab was found effective in elderly AD patients, either arising de novo in their 60s or older with no AD history by blocking Interleukin (IL)-4 and IL-13 [37]. The participant patients had showed variable onset of AD, 9 patients had senile onset, while only one patient (Pt 1) had early onset in childhood with complete remission and re-onset at the age 51 year. In elderly AD, 30% of patients have the onset in their 60s or older report they never had the disease before, another 20% had Atopic Dermatitis in childhood, while it arose in early adulthood in the rest [38,39]. This AD entity (elderly AD) is very challenging in diagnosis, because in elderly patients, Cutaneous T-Cell Lymphoma (CTCL) may look quite similar clinically to dermatitis, although pruritus is a prominent more in elderly AD, than CTCL [40]. Diagnosis of elderly AD is usually by exclusion through skin biopsy to rule out CTCL, or other itchy skin disorders disorder such immunobullous disorders (bullous pemphigoid and dermatitis herpetiformis consecutively) had been suspected in participant patients 8 and10, skin biopsies hematoxylin and eosin (H&E) had revealed spongiotic subacute dermatitis with negative direct immunofluorescence (DIF) for both diseases. Indirect immunofluorescence for BP230 and BP180 Enzyme-Linked Immunosorbent Assays (ELISAs) was negative. The elderly phenotype AD that arising de novo has a special form of dermatitis that involving face, neck and trunk while sparing the flexural areas (seen in our patient figure. 1) in contrary to AD in young age which involving flexural body areas [37]. It was reported, elderly AD is mainly extrinsic subtype possessing skin barrier impairment (high incidence of filaggrin mutations) and high serum IgE [37]. The other subtype, intrinsic AD estimates about 20% of elderly AD with female dominance with preserved -skin barrier and normal IgE [37]. Our all-participant patients had normal or little high nonsignificant total IgE (serum IgE ≤200 Ku/I) which postulated that unique AD in this specific age group might be considered as endotype, with autoreactivity to IgE, in contrary to previous findings of high IgE in elderly patients (37). Relatively an old postulated pathogenic theory in AD, that autoantibodies that target IgE have been initiated because of epitopes of human keratinocyte proteins with partly unknown function (Hom s 1-5) [40]. The previous theory (40) in this specific AD variety in elderly might explain our findings and speculated the autoimmune pathogenesis supposing human keratinocytes alteration with aging become antigenic and mimicking exogenous allergen in turn triggers IgE autoantibodies (autoantigens). A recent review provides more published studies about possible evidence on IgE autoreactivity and self-reactive T cells in children and adults with AD based on a systematic search and the possible cellular pathways contributing to disease chronicity and severity [41]. Controlling and safe therapy in elderly AD is highly challenging, because of concomitant comorbidities that mostly exist with AD [42]. Dupilumab is safe biologic therapy for AD in different age group and even for infant 6 months age [43]. Dupilumab injection had showed significant efficacy as well as good safety profile in Atopic Dermatitis of the elderly over a 16-week treatment period [44,45]. All 10 participant AD patients have been achieved proper and sustained improvement in their skin lesions morphology and pruritis inform of decreased SCORAD through treatment from W2 till W 16 with continues improvement beyond W16 Fig. 4. The improvement in clinically and marvelous decreased in pruritus since W2 of dupilumab injection in all patient which has been highly reflected positively in their life quality, reporting decreased DLQI score for them Fig. 5, which convenient with other published studies [44,45]. Dupilumab injection does not show any severe or even mild adverse reactions, fairly no complains at all from all 10 patients.

The excluded patient was female 65 years, she has elderly onset AD, no significant other comorbidities, no history of allergy to any medication. Patient had developed severe shortness of breath, skin rash with itching in the next day to Dupilumab loading dose(600mg) injection. Patient had been transferred to emergency department and her vital was not good as severe hypotension, (Bp =60/40), with rapid heart rate. Patient was managed by given intravenous normal saline, hydrocortisone and antihistamines, she discharged to home after stabilize her condition. Dupilumab injection had hold out and patient excluded from the study. An unsolicited Individual Safety Information (ISI) Report had been sent to Sanofi company reporting all details about this patient.

Conclusion

Elderly patients are the dearest to our heart, they are in sensorial need for social care and mostly for medical care due to variable comorbidities. Atopic Dermatitis in elderly a relatively recently started focused on. The etiopathogenesis in elderly Atopic

Dermatitis might be due to environmental factors influence or intrinsic immunological changes with aging process. Skin morphology in elderly AD similar to those in adult AD, with characteristic alterations like reverse lichenifation sign Treatment of this AD is tremendous challenging due to concomitant comorbidities. Pruritus is one of stressful symptoms in elderly which has huge impact on patients' life. Dupilumab is one of first biologic drug approved for AD in all age group and the first recommended treatment for elderly AD by European academy of dermatology. Our studied patients have shown initial and sustained improvement on dupilumab injection, both in skin morphology and pruritus which was reflected on DLQI improvement Dupilumab injection in elderly AD is considered relatively safe treatment, but our study is random pilot study with small number of patients. More studies needed in large number of patients in this age group that able us to establish a recommended guidelines in elderly AD.

Limitations of the Study

The small number of included patients and absence of compared control group might minimizing the results and larger controlled trials are needed for standard guidelines of dupilumab therapy in elderly AD.

Conflict of Interests

The authors have no conflict of interest to declare.

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