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The Use of Dupilumab in Atopic Dermatitis During Coronavirus Disease-19 Era – A Review

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Abstract

The global pandemic of coronavirus (CoV) d0isease 2019 (COVID-19), caused by severe acute respiratory syndrome CoV (SARS-CoV 2), has been a challenging event for every individual. It is known that COVID-19 may exhibit a vast range of symptoms ranging from mild to severe. Acute respiratory distress syndrome (ARDS) and multiple organ failure are the most common causes of death in COVID-19 cases [3]. Accumulating evidence shows that T-helper type (Th-1) inflammation cascade plays a major role in COVID-19 pathogenesis. It is proposed that aberrant immune reaction, or known as cytokine storm, is one of the main causals of ARDS in COVID-19 case, while dupilumab, the first Food and Drug Administration-approved immunomodulatory treatment for atopic dermatitis, is known for its effectiveness in suppressing the Th-2 inflammation pathway. It is postulated that both types of inflammation can cross-regulate each other. Therefore, some may believe that the regression of Th-2 cascade may upregulate the Th-1 cascade, leading to an exaggerated cytokine storm. This hypothesis leads to the uncertainty of the safety of continuing this modality during the pandemic.

Introduction

Atopic dermatitis (AD) can be deemed as one of the most common non-communicable dermatological ailments. It affects approximately 20% of children and 2–8% adults in most nations of the world [1], [2], [3], [4], [5], [6], [7], [8]. An international study shows that the figure has increased two-or three-fold within three decades in the developed countries. Therefore, it is predicted that the number will always accumulate, and this also shows that AD is a global health problem both in developing and developed nations [9].

Both personal and social aspects are greatly influenced by uncontrollable AD. For instance, the social stigma of visible skin efflorescence may affect individual's self-confidence, and debilitating itch might lower one's quality of life [10], [11]. Dupilumab, as the first Food and Drug Administration-approved biologic treatment, has been proven effective and has significantly improved quality of life. Some concerns about the safety of the utilization of dupilumab have been raised during coronavirus (CoV) disease (COVID)-19 pandemic. Some may fear that dupilumab may increase the susceptibility of acquiring COVID-19 or worsen the condition. However, it is also not recommended to discontinue dupilumab because of the chronic nature of AD and the unknown period of this pandemic [12].

In this article, the literature reviews of both clinical and immunology aspects of dupilumab in AD and COVID-19 have been explored. The aim is to provide the latest reference about dupilumab in AD patients and COVID-19. Thus, it can assist physicians in generating the best clinical judgment in a practice setting.

A Glance of AD

What is AD?

AD is defined as a chronic inflammatory skin disorder, with one of the major hallmarks of extremely pruritic, and it is very common to be found during infancy and childhood period [13]. It is crucial to bear in mind that the diagnosis of AD includes an array of major and minor features. There is no single feature that can represent AD itself nor a diagnostic assessment [14], [15] (Table 1). Many guidelines and suggestions have been published to aid clinicians in establishing the diagnosis. However, it is implied by Tada [16] that mostly adopted guideline for diagnosing both in practice settings and clinical trials is the revised Hanifin and Rajla criteria. The diagnostic can be established when at least three major features and three minor features are noted [17].

AD is a very complicated and debilitating condition, and individuals may suffer from both physical and mental issues due to uncontrollable AD. Literature shows that AD is significantly affecting all aspects of the quality of life of patients and their families [11], [18], [19] (Figures 1 and 2).

Pathogenesis

The pathogenesis of AD is subsequently complex and is not fully elucidated until now. Many theories are proposed and postulated; however, it is widely agreed that AD is orchestrated from defective skin integrity, particular genes, and dramatic response of the immune system against exacerbating factors [14], [21], [22].

In general, it is found that AD individuals' skin lacks essential genes that are needed to form a perfect skin barrier. For instance, some individuals may have filaggrin mutation; filaggrin is a gene that encodes essential proteins in building the epithelial barrier and ceramide, a lipid substance that plays an important role in retaining water permeability barrier function [22], [23] The lack of these two major materials leads to excessive trans-epidermal water loss, resulting in pH alteration and skin dryness. In addition, an antimicrobial peptide called cathelicidin, which is one of the very first layers of immune barrier, is also found to be depleted in most AD patients. [10]. Thus, exacerbating environmental stimuli such as aeroallergens, irritating chemicals, and pathogens are easier to penetrate the skin, initiating inflammation [14], [22], [24].

Th-2 type cells are widely accepted to be associated with both acute and chronic AD course [10], [14], [15]. However, Fujii [25] believes that either in acute and chronic lesion, there might be a switch from Th2 to Th1 activity.

In the acute event, interleukin (IL)-4, IL-5, IL-13, IL-25, and IL-33 levels increase [15]. Especially, in the early lesion of AD, it is shown that IL-4 and IL-13 dominate the inflammatory cascade [14], [15]. Meanwhile, in chronic AD, IL-31 has recently been discovered to be overly expressed and linked to the severity of the course.

On the other hand, it is also found that IL-4, IL-13, and IL-33 might downregulate the filaggrin, and thus, it is like a loophole of the immune system and defective skin barrier cascades [26].

Management

Overview

In general, many findings agree that the aim of the treatment of AD must be focused on inflammation cessation by repairing the skin barrier and reducing the itch. The importance of education about the nature of the ailment, skin hydration, pharmacological regime, identification, and elimination of flare causal factors is often highlighted in virtually all guidelines [10], [14], [27]. Therefore, holistic and multi-faceted approaches are needed to manage this ailment. [8], [10], [28]. The Japanese guideline for AD believes that the management of AD must be based on three fundamental aspects. First is the investigation and countermeasures of the causal and exacerbating elements. Second is the repairment if the skin defect (skincare). Last is pharmacotherapy [28]. Similarly, the European Consensus Guidelines' treatment option is quite similar to most guidelines and literature, aside from its agreement to divide the management into four phases: Baseline, mild, moderate, and severe [8]. The phases depend on the SCORing AD (SCORAD) (Appendix 1). SCORAD is one of the tools that can be used in assessing the extent and severity of AD. Less than SCORAD 25 is defined as mild, 25–50 as moderate, and more than 50 as severe. It is also suggested that in each phase, adding additional medication and antiseptic or antibiotic may be beneficial in treating superinfection.

A Brief Review of Dupilumab

Dupilumab is a human analogue monoclonal antibody that blocks IL-4 and IL-13 pathways by binding a shared α-subunit of IL-4 and IL-13, both of which are the major cytokines for Th-2 inflammation in AD [4], [29], [30].

Some experimental research demonstrated that early treatment with IL-4 and IL-3 blocking agents will dampen the responses to IFN and IL -17. In brief, when the early lesion of AD is exposed to IL-4 and IL-13, long-lasting persistent effects are doable [31]. Therefore, not only will dupilumab decrease the flare but it may also prevent the course of recalcitrant AD in the future. Dupilumab can be used either as monotherapy or combination therapy. Studies of dupilumab in 4 weeks and 12 weeks as monotherapy and as a combination with topical glucocorticoid in moderate-severe AD show significant improvement [5]. Not only were skin lesions improved but the severity of itch also rapidly decreased, allowing individuals to have a better quality of life. These results were also supported by a separate study, where Eczema Area and Severity Index score and peak pruritus Numerical Rating Score were reported to be significantly improved by the end of week 16th [32]. In terms of adverse effects, both placebo and intervention groups were almost equal [5], [32]. However, in a two phase 3 trial, it is also observed that nasopharyngitis was the second most common adverse effect after infection and infestation in the dupilumab groups [32]. A similar result is also discovered in a study of dupilumab and asthmatic patients [33].

COVID-19

What is COVID-19?

History

In December 2019, several pneumonia-like cases with unknown etiology were reported in Wuhan, China. This disease has started with suggestive symptoms of progressive respiratory infection, with some patients developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other life-threatening complications [34]. A novel beta-CoV was discovered later in January 2020 to be the culprit. International Virus Classification Commission named the virus as Severe Acute Respiratory Syndrome-CoV 2 (SARS-CoV 2), while the World Health Organization (WHO) officially named the disease as COVID-19 in the next month [1], [35]. In March 2020, the WHO asserted that this disease is a global emergency, affecting every aspect of life, and thus, declared COVID-19 as a pandemic [36] (Figure 3).

Incubation and Clinical Characteristic

Data show that symptoms of COVID-19 usually appear after an incubation period of 5.1–12 days [37]. Fever, dry cough, and fatigue are the most common symptoms. However, other symptoms such as headache, hemoptysis, and gastrointestinal symptoms such as diarrhea and vomiting are likely to be exhibited as well. In addition, dyspnea is found to be developed in more than half of the patients [1], [38], [39]. A recent study also discovered that olfactory dysfunction such as anosmia and hyposmia was found prominently in COVID-19 patients [40]. However, COVID-19 can still yield in a person without showing any symptom, which makes this ailment easily transmitted.

Route of Transmission

Human-to-human transmission is feasible due to respiratory fomites or droplets. It is also suggested that direct and non-direct contacts through mucous membrane of eyes, nose, mouth, and skin are another potential routes of transmission [39], [41]. However, a recent study discovered that aerosol transmission is highly plausible through smaller droplets or droplet nuclei. Therefore, proper inter-personal distancing and usage of mask are very essential to control the spread of infection [42], [43]. Due to a recent study that shows COVID-19 cases with enteric symptoms, it is also suggested that the digestive tract might be another possible route of transmission [44].

An article also suggests that percutaneous transmission is possible due to the high expression of Angiotensin-Converting Enzyme-2 (ACE2) in the skin tissue cells [45]. ACE-2 is known to facilitate the entry of the virus (further explanation will be explained in the next chapter). However, a thorough study is still needed to elucidate this hypothesis.

Pathogenesis

Virus structure

CoVs are enveloped with single-stranded, positive-strand RNA genome (26-32kb in weight) which comes from Coronaviridae family. There are four genera of CoVs; α, β, γ, δ, and COVID-19 belongs to the beta-CoV genus. Within beta genus itself, there are four lineages (A, B, C, and D) [3], [46].

The appearance of the virus is a rough, spherical and has prominent club-shaped elongations which contain its spike protein. This novel CoV has shown 88% similarity to bat-related SARS-like CoVs' sequence (bat-SL-CoVZC45 and bat-SL-CoVZXC21), and approximately 50% identical to Middle East Respiratory Syndrome CoVs' sequence. Due to its similar structure, the pathogenesis of SARS-CoV 2 can be postulated. However, the complete pathogenesis of COVID-19 has not been fully elucidated [47].

Table 1: Major and minor features. Adapted from Goldsmith *et al*. and Correale *et al*. [14], [20]

Major features
1. Pruritus
2. Recurrent or relapse course of dermatitis
3. Typical lesion (Facial and/or extensor rashes in infants and young children, and flexural lichenification in older children and adults)
4. Family history of atopic diatheses (asthma, allergic rhinitis, and atopic dermatitis)
Minor Features
1. Xerosis
2. Ichthyosis/palmar hyperlinearity, and keratosis pilaris
3. Immediate (type I) skin test reaction
4. Elevated IgE level
5. Early age of onset
6. Tendency toward cutaneous infections (especially staph. aureus and herpes simplex), impaired cell- mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor, and facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Relaps influenced by environmental and emotional factor
23. White dermographism, delayed blanch

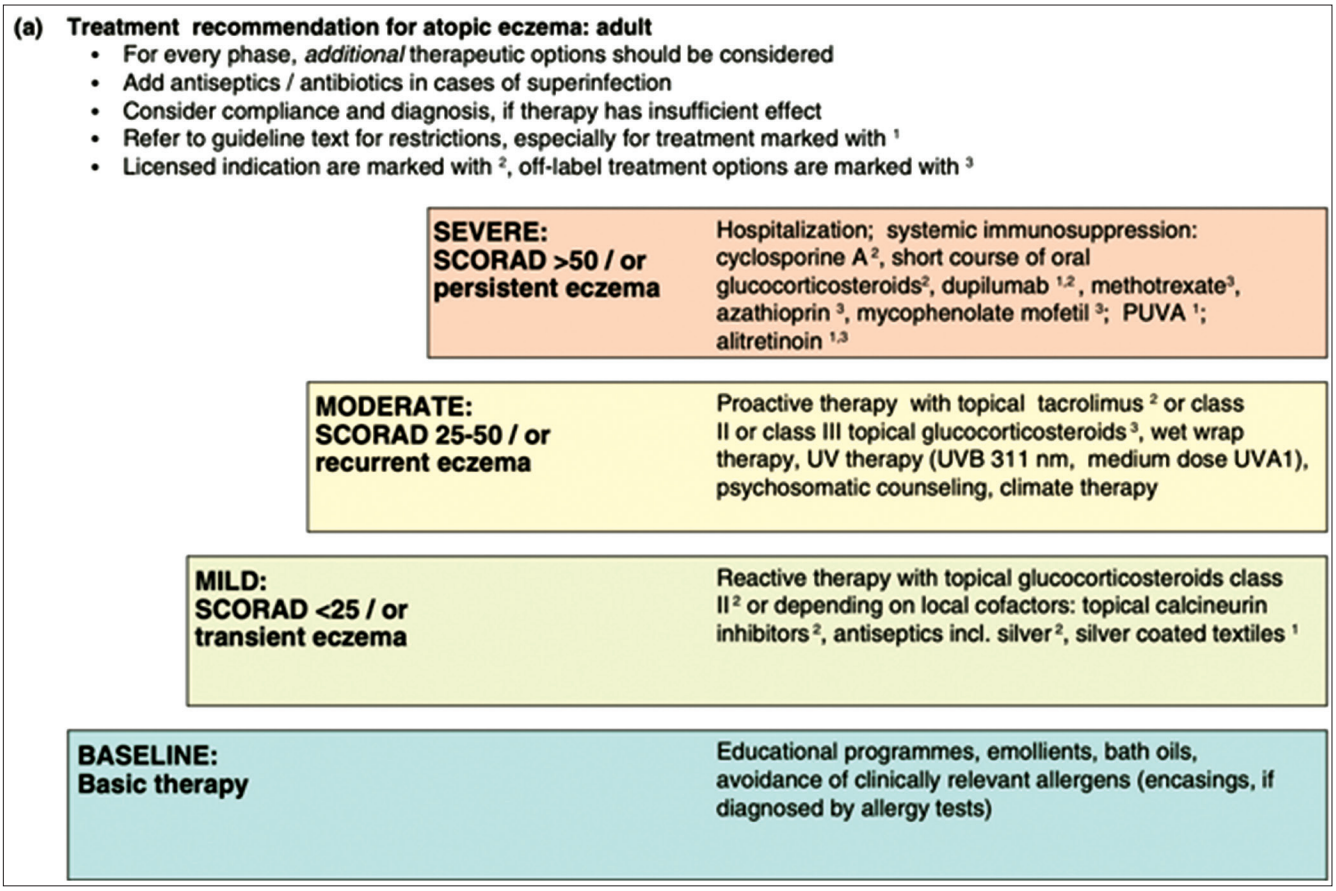

Figure 1: Management scheme of AD in adults. Adapted from Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018 May;32(5):657–82

Host Entrance and Immune Response

SARS-CoV 2 can enter the host cells by direct membrane fusion. First, the envelope spike glycoprotein will bind to the host cellular receptor, facilitated by ACE2 [48]. After entering the cell, the virus RNA genome will be released to the cytoplasm and then commenced to the replication phase [49].

Subsequently, after the virus has successfully hijacked the cells, its antigen will be presented to the antigen presentation cells. Antigen presentation will evoke host immune response which is both humoral and cellular immunity. T cells and B cells play a major role as the immune mediators in this event [35].

Since COVID-19 is caused by a virus, similar to any viral infection, the innate immune pathway is the first line of defense. However, a further aberrant and disarrayed immune response might damage the immune systems, leading to fatality [3], [50]. This event is often known as a cytokine storm. Several studies report that ARDS is the main cause of mortality of COVID-19 patients, and ARDS is one of the results of the cytokine storm [3], [51], [52]. This dramatic cytokines response makes COVID-19 difficult to manage and threaten lives.

T-helper type 1 (Th-1) cascade plays an essential role in COVID-19 infection. It is observed that cytokines that generate Th-1 pathway such as IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 rise [51]. This hypothesis is also supported by several studies and reports discovering highly expressed Th-1 related cytokines in many COVID-19 patients. For instance, a study by Huang *et al*. revealed that levels of IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, MIP-1A,MIP1-B, platelet-derived growth factor, tumor necrosis factor (TNF)α, and VEGF surge in both ICU and non-ICU required COVID-19 patients compared to healthy individuals [51].

An analyzing case study in China also saw a high expression of IL-10, IL-6, and TNF-α in severe cases compared to moderate cases [53]. An identical result is also found in a study of assessment of laboratory data reporting that IL-6 level significantly rises in severe cases compared to mild cases [54]. A multicenter study also supports previous data, in which it is observed that IL-6 was found higher in mortality cases than successful cases [55].

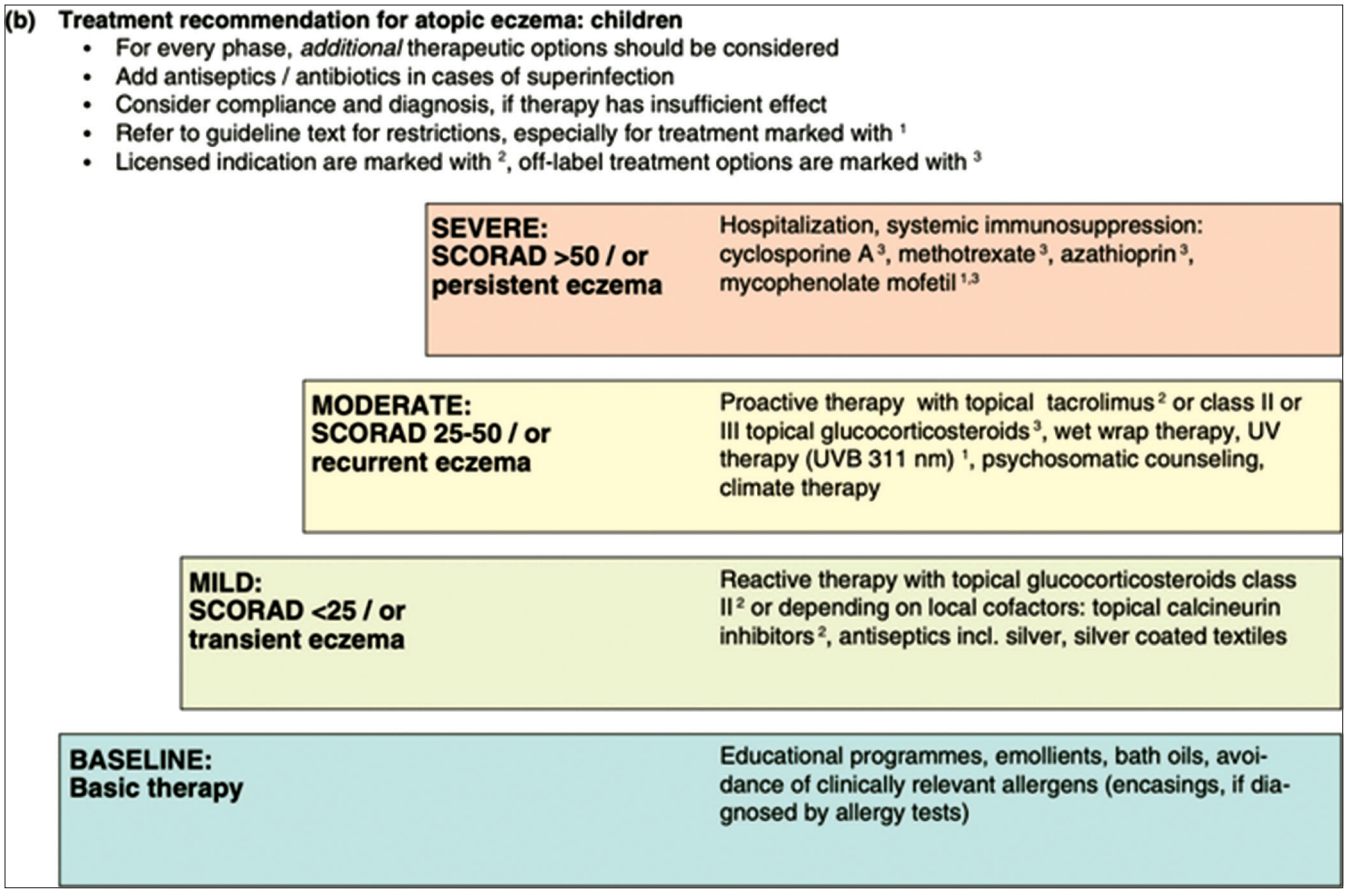

Figure 2: Management scheme of AD in children. Adapted from Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018 May;32(5):657–82

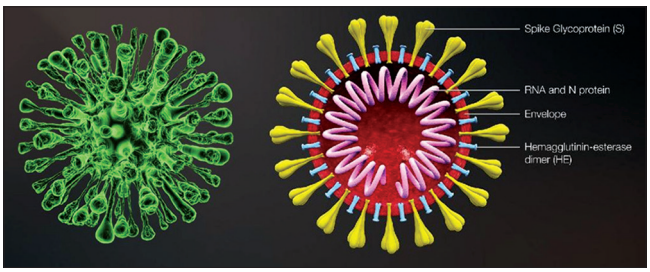

Figure 3: Structure of SARS-CoV 2. Adapted from https://microbeonline.com/sars-cov-2-properties-transmission

Discussion

Dupilumab during COVID-19 era

It is understandable that COVID-19 alters the nature of AD management with dupilumab. Some AD patients may abruptly cease the treatment or refuse to take it routinely. Some cases may be caused due to the difficulty for accessing dermatology practices that are closed during lockdown or the fear of contracting COVID-19 from clinic visit [56]. Others may have concerns about the effect of dupilumab therapy and susceptibility of acquiring COVID-19.

Even though there are some letters of statement about the usage of immunomodulators usage in dermatology cases during COVID-19 [57], [58], more sources that provide information about the safety of biologic treatment during the COVID-19 outbreak are needed [59]. Even though dupilumab is not an immunosuppressant nor steroid that might reduce the immune systems, it is postulated that immunomodulators may affect the balance of the immune system [6]. The Th1/Th2 immune balance has been studied for decades. However, it is ultimately complex and has not been fully elucidated until now. It is believed that the integration of the immune system is achieved by cell-to-cell communication, facilitated by cytokines. Therefore, it can modulate those cells to become more active (upregulate) or less active (downregulate) [7]. It is hypothesized that suppression of Th-2 polarized cytokines may upregulate the Th-1 cascade activity. For instance, IL-10 is known to release from the Th-2 pathway, and it can downregulate Th-1 production [6]. This hypothesis is also supported by a study in autoimmune disease, stating that Th-1 and Th-2 inflammations work to antagonize each other. This may be achieved either by inhibiting the production of the other cell type or by hindering each other effector function. For instance, abundant expression of IL-3 or IL-6 may block the generation of Th-1 cells from naive T cells [60].

In other words, it is plausible that the production of Th-1 polarized cytokines is upregulated due to the decreased Th-2 activity, resulting from the lower expression of IL-4 and IL-13, blocked by dupilumab. This may worsen or increase the risk of aberrant cytokine storm in COVID-19 patients. However, a study disputes that dupilumab affects Th-1 activity. It is shown that no elevation of Th-1/IFN-g-related gene expression was observed in AD patients with dupilumab [61]. Moreover, a hypothesis is also proposed that dupilumab might give AD patients more protection from COVID-19 infection. It is known that expression of IL-6, one of the infamous cytokines that play role in cytokine storm, is depended on endogenous production of IL-4, which obviously decreases in patient on dupilumab. This mechanism gives the possibility of protective effect of dupilumab in the nature of COVID-19 [62].

Many have proposed that the concept of Th-1/Th-2 immune balance is very complex and not only influenced by the cytokines profile but also by antigen presentation, immunogenic and non-immunogenic cells, genetic, hormones, oxidative stress, and environment [6], [60], [63], [64]. Thus, further research is needed to elucidate this matter.

Limitations and Recommendation

One of the limitations of this article is the sparse data of COVID-19 due to its novelty. Another limitation includes the strength of the data of dupilumab, since the most common available sources are randomized-controlled trials. In addition, most of the sources of the immunology cascades are theoretical data, and there is still little clinical evidence that can support the theory. It is recommended that physicians strictly follow-up patients with dupilumab and record their development during this pandemic.

The use of biologic modality in dermatological conditions during the pandemic may be challenging. Any decision either discontinuation or continuation of the modality may be obtained based on the evaluation of patient's profile and the risk of contracting COVID-19, particularly in high caseload zone. The continuation of biologic treatment is highly suggested with careful monitoring of any undesirable or uncommon side effects. Finally, further studies are required urgently to elucidate this matter.

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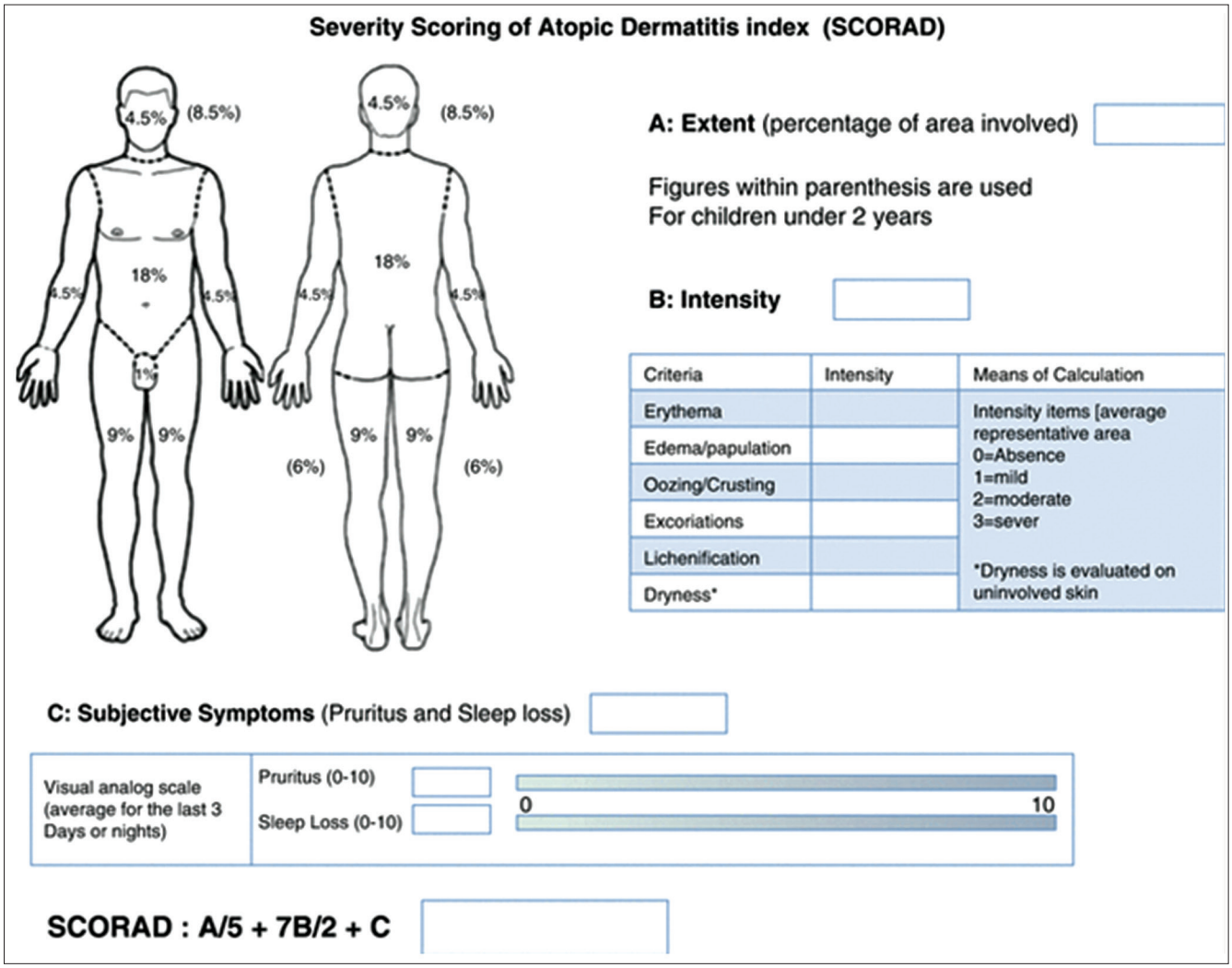
Appendix



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