

Immunopathogenesis of polymorphic light eruption, role of cytokines, effector and regulatory T-cells and its therapeutic implications

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Abstract

Polymorphic light eruption (PMLE) is mediated by a type IVc delayed-type hypersensitivity (DTH) reaction to ultraviolet radiation (UVR) induced neoantigens. While UVR normally exerts an immunosuppressive effect with increased regulatory T-cells (Tregs) and an accentuated T helper 2 (Th2) response, PMLE shows a heightened Th1 response.

Existent data in PMLE suggests a Th1-skewed immune response with reduced Treg numbers and function, lack of Langerhans cells activity, and increased CD8+ resident memory T-cells. Keratinocytes (KCs) contribute to inflammation by releasing interleukin (IL)-1 β , Vascular Endothelial Growth Factor-alpha (VEGF- α), and adhesion molecules, which facilitate various immune cell infiltration. The disturbed cytokine milieu with elevated IL-1, IL-12, IL-31, IL-36, IL-15, interferon-gamma (IFN- γ), and decreased IL-4 and IL-10, contributes to disease pathogenesis. IL-15 accounts for the recurrence of lesions.

Various drugs, including immunosuppressive agents and antioxidants, have been tried in PMLE with limited evidence. Emerging therapies include cytokine-targeting agents and Janus kinase inhibitors such as tofacitinib, which modulate cytokine milieu via Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways. Eradication of microbiota is a novel concept that mitigates the cytokine imbalance. Photohardening with narrow band ultraviolet B (NBUVB) or ultraviolet A (UVA) is believed to be effective as it enhances Treg activity. We emphasise the need for further cytokine profiling in PMLE to tailor targeted therapies, as there is an increasing evidence of a Th1 cytokine overexpression which is not curtailed by Treg cells, and thus, drugs targeting the implicated cytokines would achieve long-term results.

Key words: Cytokine, JAK inhibitors, pathogenesis, photoprotection, polymorphic light eruption, Th1, Th2, therapy, treatment, T-regulatory cells

Introduction

Polymorphic light eruption (PMLE) is a recurrent photodermatosis and is believed to be a cell-mediated, delayed-type hypersensitivity (DTH) response to a sunlight-induced neoantigen. The cutaneous immune response is mediated by an interplay of regulatory T-cells (Tregs) and effector T-cells and their associated cytokines, while recurrences are due to memory T-cells.¹⁻⁵ There are data showing that changes in the microbiome, with concomitant

expression of toll-like receptors (TLR), may play a role in PMLE.^{1,2}

Methods

We searched published literature with the key words “immunology” OR “cytokines” AND “polymorphous light eruption” using PubMed as a search engine and retrieved 62 articles using the keyword “immunology” and 22 articles using the keyword “cytokine.” Out of these, we found

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35 papers that focused on tissue or blood cytokine data in experimental or *in vivo* settings. Based on these studies, we have detailed the immunological imbalance that plays a role in PMLE and suggest the therapeutic implications of the pathway and the possible role of interventional agents.

Overview of innate and adaptive responses

The epidermis provides a physical barrier to microbial invasion. Keratinocytes (KCs) play a key role in response to pathogens and external stimuli and help regulate the immune response. Dendritic cells (DCs), present in the skin, contribute to innate immune responses and initiate a CD4⁺/CD8⁺ T-cell response to microbial and environmental antigens. DCs with putative antigens stimulate the naïve CD4⁺ T-cells in the lymph nodes, leading to the differentiation of effector T-cells and the formation of T helper 1 (Th1), Th2, Th9, Th17, Th22, or uncommitted T central and resident memory (Tcm/Trm) cells. Notably, cytokines orchestrate the development of this cell lineage. Relevant to PMLE, Th1 differentiation is promoted by interleukin (IL)-12, IL-18, interferon (IFN)- γ , and type 1 interferons, and is inhibited by IL-4, IL-10, and transforming growth factor- β (TGF- β). IL-4 determines a Th2 subtype, which inhibits the Th1 response. TGF- β and IL-2 determine Treg cells, which regulate the immune response.

Normal immune response of ultraviolet radiation

In normal individuals, ultraviolet radiation (UVR) is immunosuppressive and causes increased expression of tumour necrosis factor (TNF)- α , IL-4, and IL-10, which inhibit Th1 cell activation. Also, UVR exposure leads to the release of prostaglandin (PG) E₂, which results in immunosuppression.^{3,4} As Th1 differentiation is inhibited by IL-4, IL-10, and TGF- β , a resultant Th2 profile predominates.⁵ In addition, UVR exposure induces expansion of Treg cells, which also helps to suppress inflammatory responses.⁶

As the immune response in DTH is mediated by Langerhans cells (LCs), it is important to examine the effect of UVR on the number and function of these cells. It has been noted that UVR leads to a marked reduction in LCs (epidermal CD1a⁺ cells) with concomitant infiltration of a subset of HLA-DR1⁺/CD11b⁺/CD1a⁺ macrophages.⁷ Also, UVB induces epidermal macrophage infiltration and *in situ* proliferation of dermal dendritic cells (dDCs). This leads to a shift in immune cells in the skin, with depletion of dendritic antigen-presenting cells (APCs), which are replaced by monocytic/macrophagic cells.⁸ Also, Langerin-positive cells, which play a key role in immune responses, are depleted by UVR.⁹

There is also enhanced LC migration from epidermis to the draining lymph nodes, which is mediated by UVR-induced cytokines (IL-1 β , TNF- α , and IL-18).¹⁰⁻¹² UVB radiation also inhibits the expression of intercellular adhesion molecule (ICAM)-1, B7-2 (CD86), and major histocompatibility complex class II molecules (MHC-II) with resultant decrease in antigen-presenting capacity of LCs.¹³ A clinical effect of this is that the reduced LC activation can decrease the

responses of vaccines administered in the deltoid region, a site that is exposed to sunlight in the majority of individuals.¹⁴

Studies have also noted that neutrophils expressing CD15 and CD11b are induced after UVR, which enhances the Th2 response, preventing PMLE.¹⁵

Thus, in normal individuals, UVR affects the functioning of skin APCs, activates Tregs, increases the immunosuppressive cytokines IL-10 and TGF- β , reduces Th1 activation cytokine IL-12, increases macrophages (CD1a and CD11b), neutrophils, and mast cells, leading to a pronounced Th2 response^{4,7,16} [Figure 1]. This is also the basis of the efficacy of photohardening in PMLE.

Immune responses in PMLE

The present data suggest that in PMLE, there is a lack of UVR-induced immunosuppression, consequent to a decrease in Treg cells and a predominant increase in Th1 cells and associated cytokine response [Figure 2]. We will examine the role of various APCs and immune cells and interpret the data to elucidate the dominant cytokines and immune response.

a. Antigen

While UVR is known to be the trigger in PMLE, the antigen that mediates the tissue response remains unidentified.¹⁷ One presumed antigen is believed to arise from deficient apoptotic KC clearance, which in turn is determined by abnormal gene expression.¹⁸ The resultant protein accumulation on the cell surface leads to autoantigen formation. Similar to lupus, heat shock protein 65 (hsp65) has been implicated as a possible photo-antigen in PMLE lesions based on an experimental study.^{19,20}

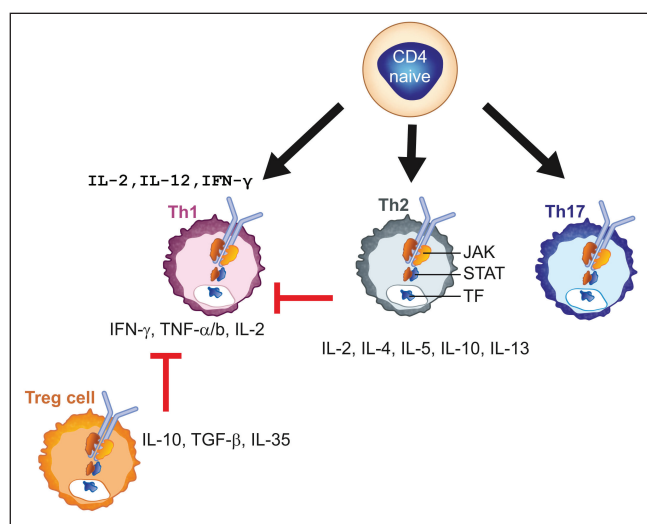


Figure 1: A depiction of normal immune response in response to UVR, where there is enhanced expression of Th2 cells in the presence of IL-4 and IL-10. These two cytokines inhibit the Th1 response. Also, there is increased activity of T regulatory cells, which suppress Th1 cells. (Th: T helper cells, IL: Interleukin, Treg: T regulatory cells, IFN- γ : Interferon- γ , TNF- α : tumour necrosis factor- α , TGF- β : transforming growth factor- β , TF: transcription factor, CD4 naive T cells, JAK: Janus kinases (JAKs), STAT: Signal transducer and activator of transcription)

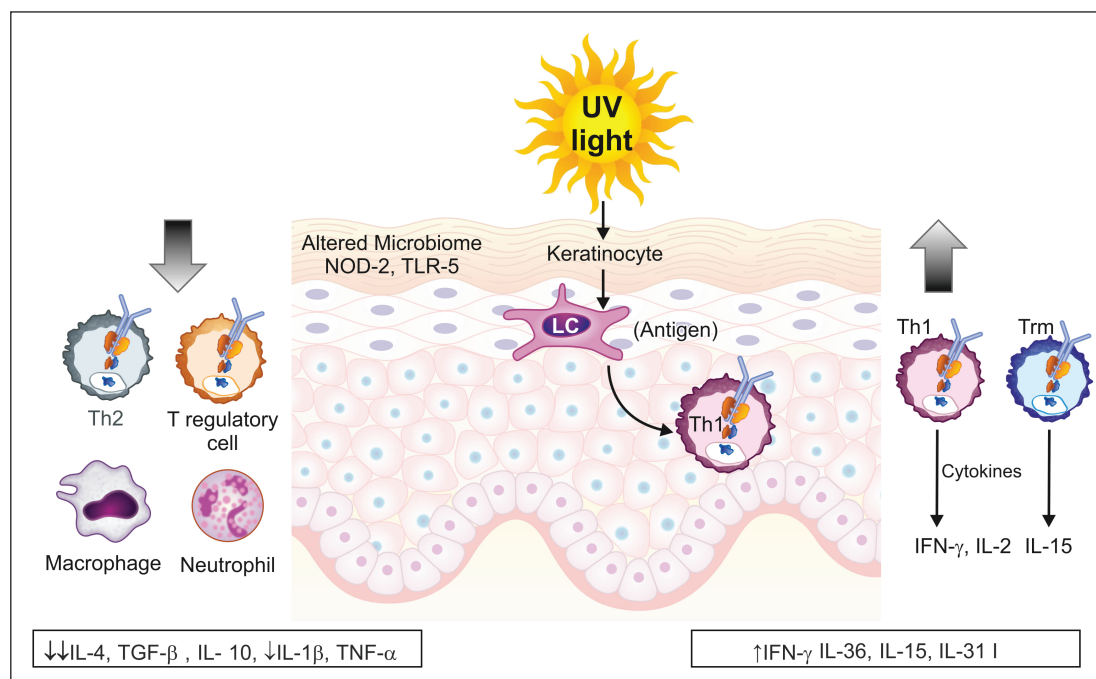


Figure 2: In PMLE, UVR and altered microbiome via Toll-like receptors (TLR) play a role in the generation of autoantigens. The cytokine milieu is determined by the keratinocytes and antigen-presenting cells (Langerhans cells), which leads to an enhanced expression of Th1 cells, which release cytokines that cause inflammation. There is also a role of resident T memory cells. There is a reduced expression and functional activity of Th2, T regulatory cells, macrophages, and neutrophils. The net cytokine expression leads to a pronounced Th1 expression. PMLE tends to resolve within a few days, the immunological mechanism for this is as yet not determined. (Th: T helper cells, Trm: Tissue resident memory T cells, IL: Interleukin, NOD2: Nucleotide-binding oligomerization domain-containing protein 2, TLR: Toll-like receptors, LC: Langerhans cells, IFN- γ : Interferon- γ , TGF- β : transforming growth factor- β , TNF- α : Tumour necrosis factor- α)

b. Keratinocytes

KCs are the first line of defence against UVR, and in PMLE, they release inactive proinflammatory precursors (pro-IL-1 α , pro-IL-1 β , pro-IL-18), which are converted into active metabolites by inflammasomes, in the presence of damage-associated molecular patterns (DAMPs). In addition, KCs release IL-10.

Studies have noted that there is a marked expression of KC ICAM-1, which starts 5 hours after UV exposure and peaks at 72 hours to 6 days.²¹ Also, vascular endothelial growth factor- α (VEGF- α) secreted by KCs induces angiogenesis and accounts for the erythema, clinical manifestation.

c. Langerhans cells and antigen-presenting cells

As stated previously, normally, UVR depletes LCs, which is not seen in PMLE.¹⁹ Hence, this functional resistance to UV-induced immunosuppression leads to a DTH response.²²

Kolgen *et al.* studied the expression of cytokines related to LC migration (IL-1, IL-18, TNF- α); Th2 responses (IL-4 and IL-10); and Th1 responses (IL-6, IL-12, and IFN- γ).¹⁹ While there was no change in Th1 cytokines, there were reduced Th2 cytokines (IL-4 and IL-10) in the UVB-irradiated skin. This led to reduced LC migration and suggested a decreased Th2 cell activity, resulting in a relative increase in Th1 activity.²³ Also, in patients with PMLE, LCs do not disappear after UV

exposure, and CD11b+ cells further increase and invade the epidermis, contributing to the development of PMLE.^{19,24}

Also, UVB leads to a transient influx of plasmacytoid dendritic cells (pDCs) with an increase in chemerin. pDCs are a subset of DCs localised to the dermis that release interferon-alpha (IFN- α) and IL-12, which further promote Th1 response.^{25,26}

d. Lymphocyte subtypes

Lymphocyte subsets can be arranged into four functional types: (i) those exhibiting proinflammatory effector properties, (ii) those with a regulatory or anti-inflammatory activity, (iii) those that promote B-cell follicle development, and (iv) those that provide long-term memory.⁵ These effector T-cells are divided into five basic groups: Th1, Th2, Th9, Th17, and Th22, which are referred to as effector cells, and are counter-balanced by regulatory T-cells, which help to control the effector cell response.

PMLE patients exhibit an accentuated Th1 response and thus exhibit an increased expression of IL-12, IL-18, IFN- γ [Figure 2]. Apart from this, PMLE patients demonstrate a decrease in Treg cell population, which in turn leads to an accentuated Th1 response.²⁷ Mast cells, which enhance Treg cell activity, are also reduced in PMLE. A study noted that while both pDCs and Treg cells are increased in lesions of PMLE (predominantly in the dermis), these Treg cells have deficient suppressor capability.²⁸ Also, PMLE frequently

recurs which is consequent to IL-15 produced by CD8+ T cells, which leads to increased resident memory cells (Trm), cytotoxic effector molecules, granzyme B (GzmB), and IFN- γ .²⁹

e. Neutrophils

PMLE is marked by a decreased skin infiltration of neutrophils, possibly leading to a diminished neutrophil-induced suppression.³⁰ This is consequent to a reduced neutrophil-derived TNF- α , IL-4, and IL-10 which lead to impaired LC migration and failure to suppress Th1 responses.³⁰

f. Macrophages

In PMLE, there is also a reduction in CD11b+ macrophages, which results in a lack of immunosuppression. Also, the infiltrating macrophages secrete IL-31, which explains itching associated PMLE.³¹

g. Mast cells

Paradoxically, mast cells are known to suppress itching induced by UV irradiation.³² In UV-exposed skin of PMLE patients, the infiltration of mast cells is reduced, suggesting that mast cells may have a role in the pathogenesis of PMLE. Photohardening also causes LC suppression, which, together with recruitment of mast cells into photohardened skin, supports the finding of mast cells deficiency in PMLE.³³

Cytokines and host immune response

Various types of effector and regulatory lymphocyte subtypes develop depending on the prevalent cytokines: IFN- γ promotes Th1 cells; IL-4, IL-5, and IL-13 promote Th2 cells; and IL-17 and IL-22 promote Th17 cells.^{5,34} Notably, the cytokines produced by specific effector cells, while promoting their own development, also inhibit other subsets. Thus, IFN- γ secreted by Th1 cells inhibits the generation of Th2 and Th17 cells, while IL-4 produced by Th2 cells promotes Th2 differentiation and inhibits Th1 cells³⁴ [Figure 1].

Notably, in PMLE, there is enhanced expression of IL-12, IL-18, IFN- γ that determines a Th1 response, IL-15 that mediates memory cell response, and IL-31 that leads to itching^{4,23,29,31} [Table 1, Figure 1]. There is also an exaggerated release of IL-1 and IL-36, with reduced expression of regulatory cytokines.³⁵ This leads to an enhanced proinflammatory cytokine state and explains the clinical morphology of PMLE.

Summary of type IVc host immune response in PMLE

In general, type IV reactions often occur in connection with shared stimulatory pathways between lymphocyte subgroups and simultaneously with multiple types of effector cells. There are four subtypes of type IV hypersensitivity reactions. Type IVa hypersensitivity is induced by a Th1-cell response and macrophage activation. Type IVb is characterised by Th2 activation with an eosinophil-driven inflammation. Type IVc involves T-cells with a stimulatory and effector cell subtype. Type IVd is defined by sterile neutrophilic effector

Cells	Cytokines
Keratinocytes	Proinflammatory (IL-1 , IL-6, IL-33, IL-36 , TNF- α) Immunosuppressive and anti-inflammatory (IL-10 , TGF- α , TGF- β , IL-1 receptor antagonist [IL-1RA])
Langerhans Cells	Proinflammatory (IL-1 α , IL-1 β) T-cell maturation (IL-12 , IL-23)
Th1 cells	IL-12, IFN- γ – Induction IFN- γ , TNF- α / β , IL-2- Effector
Treg cells	TGF- β , IL-2-Induction IL-10, TGF- β , IL-35- Effector
Trm cells	IL-15

Cytokines in bold have been implicated in PMLE. Th: T helper, Treg: T regulatory, Trm: Tissue resident memory cells, IL: Interleukin, TGF: Transforming growth factor, TNF: Tumour necrosis factor, IFN: Interferon

cell inflammation in response to CD4+ and CD8+ T-cell stimulation.

PMLE is typically a Type IVc reaction where the UVR-induced photoantigen is recognised by LCs and dDCs, which internalise the antigen and migrate via the afferent lymphatics to the paracortical area of the regional lymph node and present the antigen to CD4+ and CD8+ T-cells.^{3,7,8,17} The damage to KCs leads to the secretion of varied cytokines (TNF- α , IL-1, and GM-CSF), which activate LCs and dDCs.³⁵ The influx of immune cells is consequent to increased expression of adhesion molecules. The prevalent cytokine milieu favours a Th1 response, which, in the absence of Treg cells and increased KC-derived cytokines, leads to the local inflammatory response [Figure 2]. The abrogation of this tissue response is possibly due to the influx of FoxP3+ CD25+ CD4+ regulatory T-cells and secretion of IL-10 and TGF- β .

Therapeutic implications

The treatment of PMLE revolves around preventive strategies, the success of which depends on restoring the immunological imbalance in PMLE, which is predetermined by the cytokine milieu.^{36,37}

Apart from the use of sunscreens, phototherapy remains the most useful treatment modality in PMLE.³⁸⁻⁴⁰ This leads to normalisation of UVB-induced trafficking of LCs and neutrophils, consequent to artificial UV-B “hardening.”^{30,32,33,41} In addition, there is an increase in the number of Treg cells with enhanced FOXP3 expression, which leads to an increase in the immunoregulatory function.^{33,41,42} Notably, there is no role of vitamin D in the production and function of Treg cells, which suggests that a non-vitamin D-dependent mechanism may mediate the regulatory cell defect.⁴² Photohardening also helps restore imbalance in cytokine milieu and has been shown to decrease IL-1 β .⁴³

Topical/oral corticosteroids modulate immune responses in PMLE and are used as first-line agents [Table 2].^{44,45} Systemic steroids have an inhibitory effect on the Th1

Table 2: Therapeutic modalities in polymorphic light eruption and their immunoregulatory action		
Treatment options	Mechanism of action	Efficacy
Photohardening ^{39-43*}	<ul style="list-style-type: none"> •Normalises ultraviolet B-induced trafficking of Langerhans cells and neutrophils •Increases the number and function of T regulatory cells •Increases mast cells •Modulates cytokine milieu, significantly decreases IL-1β 	Good response (first-line treatment)
Antimalarials ^{47-48*}	<ul style="list-style-type: none"> •Increases the intracellular pH and interferes with acid-dependent cellular functions such as the processing and presentation of antigens •Reduced cytokines Inhibits expression of proinflammatory cytokines (IFN-γ, TNF-α, IL-1) •Inhibit Toll-like receptors (TLRs) (mainly TLR3, TLR7, and TLR9) 	Earlier data showed some response with Chloroquine, but this is not used due to the risk of ocular toxicity Hydroxychloroquine is slow-acting, preventive, and Controlled trials show modest benefit ⁴⁸
Glucocorticosteroids ^{44-46*}	<ul style="list-style-type: none"> •Inhibits (Th1) pro-inflammatory cytokines (IL-1β, IL-2, IL-3, IL-6, TNF, and IFN-γ) and IL-17 (Th 17 cells) •Increases Th2 cell differentiation and cytokine production 	Useful in severe cases and for short durations
Cyclosporine ^{49*}	<ul style="list-style-type: none"> •\downarrowIL-2 and IFN-γ •\downarrowIL-2, IL-4, IL-17, and CD40 (a ligand required for B-cell activation and T-cell proliferation) •It also depletes lymphocytes and macrophages in the epidermis and dermis and inhibits the activation of T-cells (CD4/CD8), natural killer cells, and antigen-presenting cells •Does not block primed T-cells or interaction with antigen 	Used as a prophylactic drug
Azathioprine ^{50*}	<ul style="list-style-type: none"> •Inhibits purine nucleic acid metabolism \rightarrow \downarrow stimulated lymphoid cells (B and T lymphocytes) •\downarrow CD8+ cells 	Used in severe cases
Thalidomide ^{51*}	<ul style="list-style-type: none"> •\downarrow TNF-α, IFN-γ, and IL-12. 	Scant data
JAK inhibitors ^{54*}	<ul style="list-style-type: none"> •Abrogates the action of 57 cytokines, including Th1 & Th2 cytokines •Reduce the expression of Trm cells via inhibition of IL-15 	Tofacitinib - Single study ⁵⁴
Other drugs ⁵³ Afamelanotide Antihistamines Carotenoids Hesperidin Nictotinamide Omega 3 fatty acids Omalizumab ⁵⁰ Polypodium Leucotomos Quercetin	<ul style="list-style-type: none"> •No effect on cytokines or immune cells 	Lack of replicable results with a lack of definitive proof of action
Potential cytokine Directed agents	Anakinra (IL-1 α and β) Nemolizumab (IL-31) Spesolimab (IL-36)	Potentially useful based on expressed cytokines in PMLE. ^{4,9-11,15,29,31,35}

*Treatment modalities which act by restoring immune dysregulation in PMLE. IL: Interleukin, IFN: Interferon, TNF: Tumour necrosis factor, Th: T helper, Trm: Tissue resident memory cells

cytokines and also increase Th2 cytokines, which play a role in PMLE.⁴⁶ Antimalarials absorb UVR in a concentration-dependent manner in the skin and inhibit the expression of proinflammatory cytokines.^{47,48} They also interfere with the functions of APCs, apart from decreasing the levels of IFN- γ , TNF- α , and IL-1, thus suppressing the Th1 response in PMLE.⁴⁷ Immunosuppressive and immunomodulatory agents such as azathioprine, cyclosporine, thalidomide, and omalizumab have been tried in PMLE with limited evidence⁴⁹⁻⁵² [Table 2]. Mechanistically, cyclosporine, with its inhibitory effect on IL-2, a cytokine that determines the CD4+ Th1 cell differentiation, seems to be an ideal drug in PMLE, although more data on its usage is awaited. Azathioprine may interfere with antigenic triggering of lymphocytes, and substitution of 6-thioiguanine increases sensitivity of cells to UVR.⁵⁰

As cytokines play an important role in PMLE [Figure 2], treatment can be directed at (i) neutralising the cytokines that promote T-effector, Th1 differentiation (IL-12, IFN- γ) (ii) blocking proinflammatory cytokines (IFN- γ , TNF- α/β , IL-2, IL-1, IL-36), or (iii) using regulatory cytokines, such as TGF- β , IL-4, or IL-10 to regulate the proinflammatory responses. Some of the drugs that inhibit the cytokine response have been detailed in Table 2.^{38,53}

While one option would be to use biologicals against the dominant cytokines, an elegant option would be the use of JAK inhibitors (JAKibs). Fifty-seven cytokines mediate their action via receptors that lack intrinsic enzymatic activity and rely on recruiting intermediary Janus kinases for downstream cell signalling. Interestingly, the cytokines implicated in PMLE - IL-15, IL-31, IL-12, IFN- γ mediate their action via JAK/STAT pathway. A recent study highlighted the efficacy

of tofacitinib in refractory PMLE patients.⁵⁴ Tofacitinib abrogates the predominant cytokine milieu in PMLE and reduces the expression of T_H1 cells, findings akin to published data in lichen planus and hand eczema, which share a similar cytokine milieu as PMLE.^{55,56}

Theoretically, certain dominant cytokines that have been implicated in PMLE may be targeted by biologics, although none have been formally tried *in vivo* as yet. Interestingly, a recent study examined the role of skin microbiota and found that in experimentally induced PMLE, there was an imbalance of cytokines and chemokines that was reversed by disinfection.⁵⁷

Conclusion

While PMLE has been known to be a delayed type hypersensitivity reaction with an accentuated Th1 response and reduced Treg activity, there is now credible evidence of increased inflammatory cytokine expression. There is an emergent need for tissue cytokine data, that can determine the effector and regulatory T-cells cytokine milieu, in the acute, chronic, and recurrent stages of PMLE. This can possibly be applied to interventions that target the dominant cytokines in PMLE. Existing data shows that the drugs that do not affect the cytokines, Th1 axis, or Treg cells tend to have inconsistent results. A classic case is that of antimalarials, where controlled trials do not show a substantial result, even though there is some data to show that hydroxychloroquine is a shade better than chloroquine. Notably, steroids and photohardening have the best results, though the former should be used sparingly in PMLE. There is as yet no drug that can simultaneously inhibit the effector cytokines and upregulate the Treg cells, which may be the ideal way to treat PMLE in conjunction with photoprotective measures.

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