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A nerve-wrecking event?

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Effects of pulsed dye laser treatment in psoriasis: A nerve-wrecking process?

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ABSTRACT

Pulsed dye laser (PDL) therapy can be effective in treating psoriasis, with a long duration of remission. Although PDL therapy, albeit on a modest scale, is being used for decades now, the underlying mechanisms responsible for the long-term remission of psoriasis remain poorly understood. The selective and rapid absorption of energy by the blood causes heating of the vascular wall and surrounding structures, like perivascular nerves. Several studies indicate the importance of nerves in psoriatic inflammation. Interestingly, denervation leads to a spontaneous remission of the psoriatic lesion. Among all dermal nerves, the perivascular nerves are the most likely to be affected during PDL treatment, possibly impairing the neuro-inflammatory processes that promote T-cell activation, expression of adhesion molecules, leukocyte infiltration and cytokine production. Repeated PDL therapy could cause a prolonged loss of innervation through nerve damage, or result in a ‘reset’ of neurogenic inflammation after temporary denervation. The current hypothesis provides strong arguments that PDL treatment affects nerve fibers in the skin and thereby abrogates the persistent and exaggerated inflammatory process underlying psoriasis (Figure 1), causing a long-term remission of psoriasis.

(Perivascular) Nerves as a target in pulsed dye laser (PDL) therapy

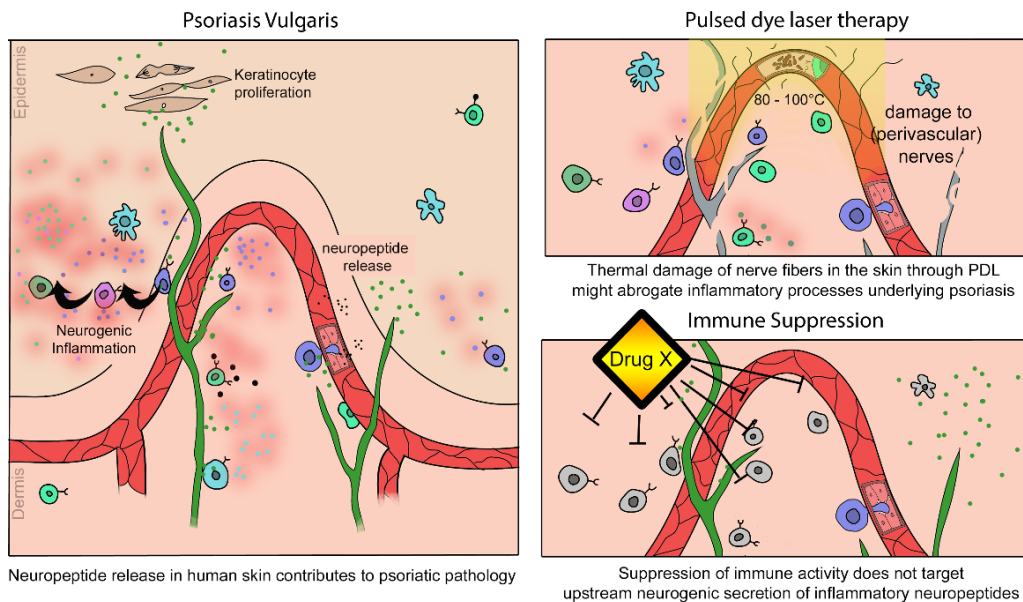


Figure 1 Graphical Abstract

INTRODUCTION

Psoriasis is a skin condition with a genetic base and a prevalence of 1-5%.¹ Current treatment strategies involve topical therapies, light (UVB and laser) treatment, and systemic medication. Despite good clinical results, vascular laser therapy such as pulsed dye laser (PDL) treatment in psoriasis is incompletely understood. Three interesting observations, as detailed in the sections below, can contribute to the understanding of the efficacy of PDL therapy in psoriasis:

- I. PDL is effective in the treatment of psoriasis
- II. Denervated skin becomes free of psoriasis lesions without any intervention
- III. The fraction of patients achieving a duration of remission of more than 12 months after completing PDL treatment is surprisingly large

We summarize the principles of selectively heating tissue using light sources and its effects on the vascular bed, and the possibility of heat dissipation to nearby structures such as perivascular nerves. We then discuss the effect of nerve injury cases on psoriasis, the inflammatory (neurogenic) processes that characterize psoriasis, and argue why suppression of nerves is an alternative target for the suppression of local immunology to treat psoriasis. Lastly, we discuss how PDL could cause a long-term loss of contact between nerves, resolving neurogenic inflammation and itch. Based on current literature, we argue that nerve damage is promising in explaining the effect of PDL treatment on psoriasis. We conclude this review by discussing the major open questions regarding the understanding of PDL treatment and future recommendations.

Principles of selectively heating the vascular bed by the absorption of pulsed light

Photo-thermal treatment of psoriasis with PDL uses light with wavelengths between 585-595 nm that is absorbed by the (oxy)hemoglobin in the blood. The selective and rapid absorption of energy by the blood causes heating of hemoglobin, and by diffusion, of the surrounding structures, heating the endothelium and the vascular wall in the (enlarged) papillary dermis for less than a second. This intense short but noxious heat (estimated to be around 60-100°C) may cause coagulation of blood vessels, rupture, and induce subsequent hypoxia.^{2,3} The number of treatments needed for remission depends among others on the location, the severity of the lesion, and on how long the lesion has been present. From the literature and our own experience,

we contemplate it is possible to clear patients with a fair skin type (Fitzpatrick type I–III) and light to moderate lesion severity after four to six PDL treatments.^{4–6}

Unlike for PDL treatment in port-wine stains, it is not established whether the decrease in (micro)vasculature is a correlation or causation in the remission of psoriasis. Two studies showed that PDL treatment altered the microvascular structure, and reduced microvascular density, which was correlated to clinical improvement.^{7,8} In another study, PDL only affected the vasculature in the upper papillary dermis, and not in the deeper, reticular dermis.⁹ In neither of the studies, it was proven that the change in vasculature was the direct reason for remission.

There is currently no obvious answer whether PDL therapy in psoriasis is merely effective because of vascular destruction, or if the vasculature functions to distribute heat to perivascular structures (i.e. perivascular nerves, collagen, free nerve endings, immune cells, basal keratinocytes). Psoriatic lesions follow the innervation pattern of the dermal nerves.¹⁰ An interesting observation is that after disruption of this innervation by trauma or disease, psoriatic lesions resolve.^{11–14} In all reported cases, the duration of remission correlated with the duration of the denervation. Nerve restoration may take several months to years, therefore posing an (unintended) ‘long-term’ remission of psoriasis. These events suggest a potential role for the localized destruction of nerves in the treatment of psoriasis. Based on current literature, we argue that peripheral nerve damage is promising in explaining the effect of PDL treatment of psoriasis.

Nerve injury resolves psoriatic plaques

Inhibiting or reducing neuropeptides in psoriatic skin may improve the lesions. We consider two types of nerves: free nerve endings and perivascular nerves. Efferent (autonomic) fibers innervate blood vessels, sweat glands and piloerectors.^{15,16} On the other hand, the afferent sensory nerve endings are important in pain and pruritus (itch) and are found in the upper dermis and/or epidermis, and may have additional branches to the vessels in the upper dermis. Upon activation of the sensory endings in the epidermis, action potentials will propagate to these deep branches, leading to release of neuropeptides and consequent neurogenic vasodilation via the axon reflex. Depending on the substance released, neuropeptides may result in neurogenic inflammation¹⁷, vasoconstriction^{18,19}, VEGF production and angiogenesis²⁰, pruritus²¹, inflammation²², mast cell activation²³, or alter expression patterns in other cells²⁴, depending on the substance released (substance P, calcitonin gene related peptide, neuropeptide-Y, *etc.*).^{25–29}

Lesional psoriatic skin harbors $\pm 40\%$ more nerve fibers compared to non-psoriatic skin.³⁰⁻³⁴ Greater nerve growth in psoriasis skin may relate to increase presence of nerve growth factor (NGF) in the skin. NGF is recognized both as a neurotrophic and pleiotropic factor that is produced by a variety of cells, including keratinocytes and immune cells.³⁵ NGF has functions in nerve support and growth and also promotes keratinocyte proliferation. NGF showed a ten times higher expression in cultured human keratinocytes from psoriatic skin compared to healthy skin cells.³⁶ Similarly, blocking NGF in human skin-transplanted mice improved outcomes for psoriatic lesions³⁷, suggesting that NGF and support of neurite growth plays an important role in the hyper-proliferation of keratinocytes, which is a hallmark in the pathogenesis of psoriasis.

NGF is also produced by endothelial cells and involved in endothelial cell proliferation and expression of endothelial adhesion molecules.³⁸⁻⁴⁰ Endothelial adhesion molecules facilitate leukocyte infiltration, and upregulation allows for more extravasation of inflammatory cells. Another important molecule in neuro-inflammation and endothelial leukocyte transmigration facilitation is Substance P (SP). Exposure of SP to endothelial cells resulted in a significant increase of ICAM-I and VCAM-I molecules *in vitro* which coincided with increased leukocyte adhesion to SP-exposed endothelial cells³⁸. The same study also showed *in vivo* that the topical application of neuropeptide-releasing agent capsaicin on human skin increased ICAM-I and VCAM-I in the microvasculature.³⁸ Furthermore, SP is involved in mast cell degranulation and consequent production of VEGF and TNF-alpha, vasodilation, and increased microvascular permeability.^{26,41,42} Both substance P⁴³ and NGF³⁶ are upregulated in active psoriatic skin lesions. Interestingly, expression of endothelial adhesion molecules (ICAM-I, E-selectin, and $\alpha V\beta 3$ integrin) decreased 40-75% after PDL treatment of psoriasis.^{5,9,44} We suggest it is plausible that the deprivation of molecules related to neuro-inflammation through hyper-thermal denervation by PDL treatment relates to the improvement or remission of the psoriatic plaque. As supporting evidence, a single treatment with the PDL for rosacea was associated with a significant decrease in epidermal nerve fiber density⁴⁵, and a decrease in substance P.⁴⁶

Psoriatic inflammation

The immune system in psoriatic skin is over-activated and sustains dermal inflammation.⁴⁷⁻⁴⁹ The current understanding of psoriatic immunopathology is based on a chain reaction of T-cell activation and a subsequent cytokine storm.⁵⁰ TNF- α , IL-17, and IL-23 play a major role in the onset and persistence of psoriasis.^{51,52} IL-

23 induces the expression of cytokines and differentiation of other (CD4⁺) helper T-cell subsets like Th1 and Th17, leading to the production of TNF- α and IFN- γ .^{53,54} Cutaneous nerves contribute partially to inflammation through the (uncontrolled) release of neuropeptides. The *in situ* expression of many neuropeptides is elevated in psoriatic lesions, and because of the strong interaction with the immune system, provokes neurogenic inflammation.^{22,27,36,55,56}

Neurogenic inflammation in psoriasis

The role of nerve fibers in psoriasis-related inflammation is sustained in many current reports (reviewed in Zhang et al. 2020⁵⁷). TRPV1⁺ neurons were identified as free nerve fibers and also present surrounding the blood vessels in the rat.⁵⁸ Furthermore, TRPV1 channels were also localized in mast cells, epidermal keratinocytes, dermal blood vessels, and other structures in the skin.⁵⁹ Unlike in rodents, TRPV1⁺ nociceptors constitute around 60-70% of all human sensory neurons.⁶⁰ Additionally, another study reported that TRPV1 is upregulated in pruritic lesions of psoriasis.⁶¹

TRPV1 knockout mice showed a decreased psoriasiform inflammation in response to topical application of imiquimod (IMQ), which was characterized by a decrease in skin hyperplasia, a decrease in angiogenesis, and less infiltration of leukocytes into the skin with lower levels of IL-1B, IL-6, and IL-23.⁶² More specifically, Riol-Blanco *et al.* (2014) showed that suppression and/or ablation of TRPV1⁺ nociceptive nerves in mice skin prevented the production of IL-23 and subsequent infiltration of immune cells into the skin after application of IMQ. In the same study, intradermal injection of IL-23 bypassed the necessity for TRPV1⁺ nerves and restored the IMQ-induced inflammatory response.⁶³ These findings indicate that TRPV1⁺ nerves are essential in the IL-23 production and onset of inflammation in the psoriasis-like IMQ model in mice. In another study, topical application of capsaicin attenuated the onset of psoriasiform inflammation in the IMQ-mice model and RT-PCR revealed decreased expression of IL-6, IL-17A, IL-22, IL-23 and TNF- α .⁶⁴ Thus, reducing the neuroinflammatory effects of nerves in the skin may aid in improving psoriatic symptoms but little experimental research has been published on this topic.

One study indicated that two PDL treatments resulted in over 50% decrease in expression of IL-23 and TNF- α in psoriatic skin but did not study the nerve densities in the skin.⁵

Collectively, these studies have shown a relationship between TRPV1⁺ nerve fibers and onset of psoriasiform inflammation and corresponding cytokine production,

implying that removal or functional normalization of TRPV1+ neurons in the skin might reduce important psoriasis-related inflammatory factors. Future research on the interaction between TRPV1+ and inflammatory cells might provide a more detailed mechanistic explanation of the role of nerves in onset and remission of psoriasis.

Suppression of local immune responses through classic psoriatic drugs

Suppression of local immunology is one of the major drug-treatment strategies applied in psoriasis. Many of these drugs directly target important immune regulators, such as IL-17, IL-23, or TNF- α ^{65,66}. These drugs need to be administered continuously to have the desired effect. Continuous administration results in patients being dependent on long-term drug adherence in order to be free of psoriasis. Long-term systemic immune suppression also increases the risk of soft-tissue infections, tuberculosis, hepatitis B, and increases the risk of skin cancer.⁶⁷ Despite the clinical efficacy of topical applications or systemic treatment that suppress the immune system, discontinuation of the drug results in a relapse of psoriasis, usually within six months.⁶⁸ Hence, current treatment strategies would benefit from a treatment option that would allow for a drug-free remission of psoriasis. Perhaps, finding an alternative treatment target that is upstream of the inflammatory pathways would aid in the search for drug-free remission of psoriasis.

One such upstream target could be the dermal nerves that inflict neurogenic inflammation. Inhibiting these nerve fibers may reduce neurogenic inflammation in the skin. Several findings are in line with this statement. The use of capsaicin (agonist to TRPV1) resulted in a decrease in psoriatic lesion severity and inflammation.⁶⁹⁻⁷² Intrathecal injection of 10 μ g capsaicin in mice eliminated TRPV1+ nerve fibers and neuropeptide CGRP.⁷³ Silencing TRPV1 increased the expression of anti-inflammatory factors *in vitro*.⁷¹

Regrowth of nerves is complex and time-consuming

Damage to the skin and subsequent wounding of the skin tissue may also involve damage to peripheral nerves. Wound healing involves many complex processes, in which peripheral and perivascular nerves play a role because they secrete neuropeptides and neurotrophins that interact with immune cells. Indeed, damage to nerves inhibits wound healing⁷⁴ and regeneration is complex and slow.⁷⁵ Successful restoration of nerves depends on the navigation of the axon through the extracellular matrix that contains inhibitory molecules (chondroitin, other glycosaminoglycans), to the disconnected part of the distal nerve which is usually hallmarked by stimulatory molecules for nerve (re)growth (NGF, BDNF, NT3).⁷⁵⁻⁷⁷ Following

wallerian degeneration of the distal sensory endings, subsequent restoration of these endings is prospective when remains of the myelin sheath are still intact.⁷⁸ Myelin sheaths are present around the larger nerve fibers, A β and A δ , but not in terminating free nerve fiber endings (C-fibers). However, c-fibers are supported by unmyelinating schwann cells and Remak bundles that occupy a supportive role in nerve regeneration.⁷⁹

PDL treatment coagulates vessel walls and/or red blood cells in the upper dermal plexus (mean 0.37 mm and max 0.65 mm of depth for vessel wall coagulation and on average 1.16 mm depth for blood vessel coagulation⁸⁰) resulting in a temporary decrease in oxygenation, a deteriorated nutritional environment, and waste build-up in the skin. Proper vascularization is required for nerve regeneration as Schwann cells are recruited by VEGF and use blood vessels to orchestrate the restoration and reconnection of nerves.^{81,82} It is known from nerve grafting research that vascularity of the nerve relates to increased numbers of Schwann cells and minimal intraneural fibrosis.⁸³ Furthermore, many studies on scar research have demonstrated that PDL can alter the extracellular matrix, by increasing or decreasing collagen types and expression levels of matrix metalloproteinases (MMPs).⁸⁴⁻⁸⁸ Thus, disruption of the vasculature and/or surrounding cellular matrix components by PDL treatment possibly creates an unfavorable environment for nerve regeneration.

It is currently unknown what the reinnervation time is for psoriatic nerve fibers after damage to the upper layer of the skin (max 1.2 mm depth⁸⁹), where PDL therapy is thought to have an effect. Studies using a single 30-minute 8% capsaicin treatment on diabetic skin showed that reinnervation started around three weeks.⁹⁰ Full recovery of innervation in healthy human skin after a 60-minute single application of capsaicin comprised 24 weeks.⁹¹ More studies are needed as PDL treatment may act differently on the skin compared to capsaicin, and because psoriatic skin is typically hyper-innervated compared to normal or diabetic skin. A single PDL treatment is unlikely to cause prolonged denervation. However, repetition of treatment within an optimized time frame might increase the chances of semi-permanent denervation as time-dependent regeneration and reconnection processes involve molecules that are secreted in a limited time frame (mTOR, GAP43, etc).^{92,93} Therefore, the reinnervation time of the skin after PDL could be relevant to optimize the time between treatments.

The onset of chronic denervation is around eight weeks after peripheral injury, and regenerative support for axons is ending at four to six months post-injury.⁷⁷ Delayed regeneration of nerves resulted in a decrease in the number of nerve fibers and

reduced nerve fiber length.^{94,95} In most cases, reduced innervation is undesired but in psoriasis, a reduction of the abundant nerve fiber density may have desirable effects. Above, we discussed that nerve injuries resolve psoriasis, that psoriatic skin contains more nerve fibers, and that nerves sustain psoriatic-related neurogenic inflammation. Laser therapy for psoriasis thus does not necessarily constitute total denervation, but rather a restoration of normal innervation of the tissue. Damage to blood vessels upon PDL and consequent impaired supply of oxygen, nutrients, and immune cells could impede the delicate regeneration of nerves similar to those in normal wounds. Repeated PDL therapy could cause a prolonged loss of contact between the distal nerve part and the soma. As such, PDL therapy potentially causes a controlled and gradual denervation of the skin that resolves neurogenic inflammation and itch. A study in rosacea patients showed that three months after PDL therapy, the number of nerve fibers was significantly lower than before the laser treatment.⁹⁶

Final hypothesis: PDL therapy normalizes innervation of the skin and inhibits neurogenic inflammation

The purpose of this review was to explore the potential role of nerves in PDL treatment for psoriasis. We started with the understanding that the remission times of PDL are surprisingly long compared to other treatment strategies, and that similar long-term remission is observed in accidental nerve injuries. Our main hypotheses and/or notions are that (1) the nervous system and immune system stimulate each other to maintain neurogenic inflammation, which resembles immunologic features of psoriasis. (2) Inhibition of, or injury to, nerves improves psoriasis. (3) PDL therapy coagulates blood vessels and possibly affects perivascular nerve structure and function. (4) The obstructed vasculature results in a depleted microenvironment

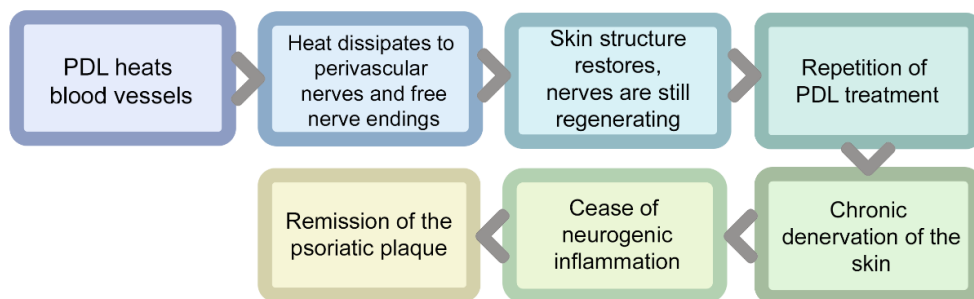


Figure 2 Proposed working mechanism of PDL treatment for the long-term remission of psoriasis

delaying and impeding full nerve regeneration. (5) This may allow for a ‘reset’ of neurogenic inflammation of the skin. We further hypothesize that the repetition of PDL treatment would be crucial to prevent full nerve restoration and to cause a controlled long-term normalization of the nerve distribution in the skin (Figure 2). Similarly, we expect that insufficient blood vessel coagulation and/or nerve injury underlies unsuccessful PDL treatments. Consequently, PDL treatment should be continued and maintained until a significant reduction of psoriatic hallmarks (erythema, itch, scaling) is effectuated.

Major Open questions

Many aspects of PDL therapy are undescribed or currently unknown. One open question is how nerves are targeted while other structures remain intact. The simplest explanation is that neurons are denatured upon heating of the blood vessels in PDL treatment, given that the temperature is sufficiently high. It is unknown what the role of TRPV1 is within PDL treatment, and the consequent heat dissipation, may target TRPV1+ channels (43°C) in the skin. A similar channel, TRPV2 is activated by noxious temperatures from 52°C and is present on neuronal cells and on a wide variety of immune cells.^{97,98}

Activation of these TRPV channels results in the influx of Ca^{2+} .⁹⁹ Too high intracellular calcium levels in combination with ischemia can cause mitochondrial damage¹⁰⁰, cell swelling, and neuronal death.¹⁰¹ Despite TRPV1/2 channels being an interesting therapeutical target it is unknown whether a subsecond delivery of energy, inducing a short and transient activation of TRPV1/2 channels, would lead to a calcium influx that is sufficiently large to cause the above processes, and this remains to be further studied.

Besides the possibility of thermal damage and disintegration of perivascular nerve fibers, secondary effects of PDL may aid in therapeutic denervation, such as the activation of anti-inflammatory heat shock proteins, temporary edema, ischemia, and/or local nutrient depletion due to vascular disruption. There is currently no literature regarding the contribution and importance of the above-mentioned secondary effects of PDL. Studying the side effects of PDL that aid in neuronal degeneration is crucial to further confirm our proposed model. In the context of chemotherapy-induced neuropathy, the mechanism of pain relief by capsaicin may involve the regrowth of healthy nerve fibers rather than only denervation.¹⁰² Likewise, it is possible that the effect of PDL involves not only reduction of nerve fiber density but also regrowth of less pro-inflammatory fibers. This warrants studies on not only fiber density but also on the phenotype of these fibers after PDL treatment.

Incorporating the suggested mechanism of vascular denervation would spare the epidermal branches and preserve sensory function while reducing axon reflex vasodilation and neurogenic inflammation. Indeed, to date there is no evidence or research indicating that the skin becomes insensitive after undergoing PDL treatment. It is plausible that PDL does not affect nociception as these nerves are farther away from the blood vessels that are heated up by the PDL treatment, which mainly affects perivascular nerves. Further research including immunostainings of the skin is necessary to confirm and quantify decreases in nerve density in psoriatic skin after PDL treatment.

Based on recent literature and the proposed working model of PDL in this paper, PDL may have multiple applications. Over the years, PDL treatment has broadened from treating port-wine stains to psoriasis, to other conditions such as rosacea, eczema, urticaria¹⁰³. Based on our assumptions, we suggest the possibility that PDL treatment may be useful in chronic itch and other diseases with increased or abnormal activity of nerve fibers. Thus, PDL may be implemented and combined within multiple treatment strategies of pathologies that benefit from a change (e.g. reduction or normalization) of nerve fibers and/or neurogenic inflammation. More experimental research is needed to determine the variety of pathologies that may be aided with PDL treatment, especially those that are in lack of sustainable treatment options.

Conclusions and perspectives

From a clinical perspective, administering PDL treatment as a sole treatment may be inefficient in wide-spread lesions, large body surface area (BSA), or refractory areas

like genitals and scalp. A major limitation of PDL is the labor intensity, as laser treatment is time-consuming when it comes to larger plaque areas. Instead, the current application of PDL is probably most effective as an additional treatment to standard therapy, topical treatment, oral medicine, JAK inhibitors, and cyclosporine. PDL therapy can be an effective treatment option for cases where psoriasis is of limited surface area, or for hard-to-treat locations as elbows and knees. Despite its specific appliance, PDL therapy has been shown effective in the treatment of psoriasis and can lead to remission times that are surprisingly long. Similar long-term remission of psoriatic lesions can be observed in nerve injuries. These observations led us to the hypothesis that nerves are important in psoriasis. Indeed, cutaneous nerves secrete a plethora of neuropeptides, which initiate processes such as cytokine production (IL-17, IL-22, IL-23, and TNF-alpha), keratinocyte proliferation, and angiogenesis. Commonly used treatment strategies involve the suppression of the immune system, especially of IL-17 and IL-23, and improve the psoriatic lesion. Despite clinical efficacy, discontinuation of the drug results in a return of psoriasis. Thus, an additional treatment strategy could be to target the upstream production of neuropeptide release through partial nerve injury. The learning point of this review is that PDL treatment may affect the (perivascular) nerves by dissipating heat, as these nerve fibers are closest to the blood vessels that are targeted by PDL. In addition, the extension of heat distribution of the skin is determined by the laser settings. Short pulses (0.45 ms) will result in a more selective effect, focusing the absorption of light around the blood vessels, whereas longer pulses (1.5 ms and up) will cause more bulk heating of the skin. Nerve restoration is a long-term process, and long-term nerve injury may be the result of repeated PDL treatment. Further research should provide a better understanding of the mechanisms underlying psoriasis remission, and the role of nerve fibers therein, potentially leading to tailoring laser treatment protocols to various plaque severities, lesion history, and/or body location of the plaques. This would allow future treatment protocols to achieve efficient and long-lasting remission of psoriasis with fewer treatments.

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