Photobiomodulation as potential novel third line tool for non-invasive treatment of Hidradenitis Suppurativa

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Abstract

Hidradenitis Suppurativa (HS) is a severe inflammatory pathology of the skin characterized by chronic recurrent inflamed lesions, nodules, sinus tracts and abscesses usually manifests after puberty, which involves scalp, neck, axillae, perineum and infra-mammary areas. Nowadays treatment options range from short or long courses of antibiotics, anti-inflammatory and biologic drugs, to surgery. Other suggested treatments consider the employment of laser devices, mainly microsurgical lasers (such as CO_2 and intense pulsed lasers) and photodynamic therapy. This review explores the potential use of photobiomodulation (PBM), already used for the treatment of other skin conditions, such as acne, hypertrophic scars, wrinkles, and burns, as potential novel therapy for HS. PBM has been reported to have beneficial effects on promoting wound healing, angiogenesis, vasodilation, and relieving from pain and inflammation, as recently demonstrated in an *in vitro* model mimicking HS disease. In addition, PBM, specifically set at the blue wavelength, has been recently reported as exerting an anti-bacterial activity. Therefore, considering all these PBM features especially its ability to decrease pain and inflammation and to lead to faster wound healing, thus improving patients' quality of life, we hypothesize its employment as adjuvant third line treatment for the management of HS both in young and adult patients.

Keywords: Hidradenitis Suppurativa; wound healing; photobiomodulation; laser.

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1.   Introduction

Hidradenitis Suppurativa (HS) is a chronic skin disease lacking treatments able to finally eradicate the pathology; indeed, currently available treatment options consist of several types of medication and surgical management, but the patient's response and outcome are various and not conclusive. The present study aims at suggesting photobiomodulation (PBM), which employs laser light to biostimulate intracellular processes, as novel potential tool to decrease pain and inflammation and to support wound healing management, particularly after skin surgical excision. Since no previous research groups utilized the PBM to treat HS affected patients or to pre-clinically test it on animal model, this review should be considered as a theoretical proposal, based on rational considerations and supported by our recent findings obtained in HS keratinocytes *in vitro* model where PBM was able to exert a beneficial outcome in terms of inducing cells migration but not proliferation. Nevertheless, we think that PBM, thanks to its beneficial impact on different skin affections, as acne, hypertrophic scars, wrinkles and burns, could be a third line adjunctive option, together with other recommended treatments, to treat HS patients, both in young and adult patients.

2.   Hidradenitis Suppurativa

Hidradenitis suppurativa (HS), often designed as acne inversa, is a chronic, recurrent, debilitating, follicular inflammatory skin disease. It features painful, deep-seated, chronic, suppurating lesions most commonly in the axillary, inguinal, ano-genital and infra-mammary regions [1] associated with strong feelings of shame leading to isolation and depression [2]. To place the HS related morbidity into perspective, HS scored one of the most elevated Dermatology Quality of Life Index (DLQI) among other important dermatoses [3]. This disease is not rare as it affects 1-4% of the general population, and usually manifests after puberty [4]. However, in young children it is still present, especially with a history of parents with HS. Paediatric patients often display hormonal imbalance and the disease affects similar areas as the adults, but therapies in these young patients are not well studied [5].

The pathophysiology of HS is the result of a complex interplay between genetic and environmental factors cross-talking with both innate and adaptive immunity dysfunction [6,7]. Heterozygous mutations in the γ-secretase genes – presenilin enhancer 2 (PSENEN), presenilin (PSEN1) and nicastrin have been associated with both sporadic and familial cases of HS [8,9], with obesity and smoking acting as main aggravating factors [2,10].

The above mutations cause inactivation of Notch signaling which is responsible for an altered homoeostasis of hair follicle and apocrine gland leading to the production of the so-called damage-associated molecular pattern (DAMP) molecules. These molecules induce an abnormal activation of the inflammasome, a molecular platform triggering the inflammatory process in HS as in the classic monogenic autoinflammatory diseases like familial Mediterranean fever [11]. The important autoinflammatory component in the pathogenesis of the disease is supported also by the upregulation of interleukin(IL)-1β [12,13], which is a pivotal cytokine in autoinflammation [14]. On the other hand, some studies found γ-secretase mutations only in a minority of HS cases [15,16] suggesting γ-secretase mutation alone is not sufficient to produce the HS phenotype [17]. Interestingly, our group reported mutations involving a number of autoinflammatory genes in the recently described syndromic variant of HS known as PASH (pyoderma gangrenosum, acne, suppurative hidradenitis) [6,18], giving rise to considering HS a polygenic autoinflammatory condition in which innate immunity dysfunction plays a key role. From an immunological point of view, IL-17, cytokine merging innate and adaptive immunity, has also been reported overexpressed in the lesional skin of HS [19]. Of note, with respect to IL-1β and IL-17 expression, HS resembles PASH [20] as well as two prototypic neutrophilic dermatoses, pyoderma gangrenosum and Sweet's syndrome [21], making justified, to include HS in the spectrum of neutrophilic dermatoses [22], based also on the high number of skin infiltrating neutrophils especially in later stages of the disease [12].

Bacteria released after hair follicle breach can amplify a pre-existing subclinical inflammation [23,24] and also activate autoinflammation as exogenous stimuli [11]. In this respect, Guet-Revillet et al.[25] evidenced the existence of two profiles of opportunistic bacterial pathogens associated with HS. In the first group, including mainly patients with less severe HS, *Staphylococcus lugdunensis* was the unique or predominant bacteria colonizing nodules and abscesses, whilst in the second group a mixed anaerobic flora containing actinomycetes and streptococci of the milleri group were isolated from sinus tract and fistulas. Noteworthy, as the authors pointed out, these bacteria have been already concomitant to infections of the skin or other soft tissues, but due to their low pathogenicity, they require an underlying predisposing condition of the host to be harmful. The same influencing condition has been assumed also in different findings by Kathju et al. [26]. As far as pain is concerned, HS affected patients report different forms of pain: inflammatory, non-inflammatory, neuropathic, ischemic and pain related to arthritis; also depression has been described [27,28].

2.1. Treatment

The involvement of typical areas together with the presence of chronic and unremitting lesions, are the only available criteria to diagnose HS. Moreover, HS is notoriously difficult and challenging to treat, requiring the intervention of different medical specialists such as dermatologists, emergency doctors, internists, and plastic surgeons.

Lack of molecular tests to diagnose HS and relying on sole clinical symptoms causes a severe delay (median of about 7.2 years) in HS diagnosis [29]. During this time patients are often treated for different disorders often bouncing from one treatment to another without a clear rationale. Most of the patients, waiting for a diagnosis, receive treatments for severe acne ranging from exfoliants (mainly resorcinol) to retinoids (isotretinoin). Topical antibiotic treatments are prescribed to the majority of the patients aimed at managing the folliculitis, mainly chlorhexidine lotions or clindamycin 1% solution [30]. Furthermore, in the absence of a definitive diagnosis, many patients undergo surgical drainage of the abscesses, often reiterated.

Once the HS diagnosis is made, patients are usually treated by a systemic therapy with antibiotics. A recent survey showed that UK dermatologists use tetracyclines as first-line oral therapy [31], whilst they prescribe as a second-line therapy a combination of rifampicin-clindamycin based on small case series [32].

Today, HS patients are usually treated with a long or short course of a combination of antibiotics, mainly rifampicin-clindamycin [32] or rifampicin- moxifloxacin –metronidazole [19], and then lesions are surgically excised.

Several surgical treatments, tailored on the severity of the disease, co-exist and they can be recommended accordingly to the literature [33], being each method tailored on the severity of the disease. Several surgical approaches to reconstruct the affected tissues, among them conventional surgery with incision and drainage, electrosurgical de-roofing and CO_2 laser techniques, are widely employed [33,34]. The current guidelines agree in starting the surgical approach only when HS patients are in the remission phase of the disease, so this treatment is part of a multidisciplinary approach to reduce HS symptoms in view of the surgery. The Algorithm of Kagan et al. [35] has been designed to select the best surgical approach in patients with HS.

Lately, FDA approved the use of the tumour necrosis factor (TNF)-α antagonist adalimumab in the treatment of moderate-to-severe HS [36], which is supported by reports of overexpression of TNF-α in the lesional skin of HS [12,13] and by the elevated circulating levels of this cytokine in the disease [37]. Moreover, other biological treatments for HS, such as the blocker of the IL-12/IL-23 axis ustekinumab and the IL-1 receptor antagonist anakinra, are at

present time under consideration [38]. A trial on the IL-17 inhibitor secukinumab in HS is ongoing on the basis of its proven efficacy in anecdotal cases of severe disease [39] .

3. Lasers for HS treatment

The lasers formerly employed for HS treatment are surgical or microsurgical, being able to cut tissues (CO_2 lasers), to destroy hair follicles (intense pulsed lasers, IPL) [34] or to damage tissues trough the usage of photosensitizers (photodynamic therapy, PDT) [40].

Despite the beneficial outcomes derived from the application of laser light, the patients sometimes felt pain in the irradiated wounds with the need of assumption of analgesics or of cooling the treated area. Additionally, some authors describe the onset of adverse effects, such as scars or skin photo-toxicity with the development of erythema or edema [41,42].

So, other treatments that could be useful and efficacious to heal HS phenotypic manifestations and to manage skin lesions after surgery are envisaged.

In the field of medical lasers, the most frequently used mechanism of photon energy conversion is heating, which can be exploited for tissue destruction, such as for cutting, vaporization, coagulation, and ablation. On the other hand, when using low power settings, the thermal effect is minimum and photochemical conversion of the energy is prevalently absorbed by photoacceptors [43]. This means that cells contain intracellular molecules, able to respond to laser light, probably differently for each wavelength, thus being capable to activate specific metabolic pathways. This approach refers to the laser therapeutic activity and it is called "photobiomodulation" (PBM)[43].

The following sections will review the literature on the use of surgical lasers in HS and will explore the properties of PBM.

3.1. CO_2 laser

CO_2 lasers (10.6 μm wavelength) are usually employed to selectively ablate affected skin areas through thermal effects, specifically by excision and vaporization. The first technique can be used to excise the entire damaged area, while the second one selectively destroys nodules, abscesses, and fistulas, without damaging the surrounding healthy tissues. Beginning from the lesion center, the tissue is vaporized gradually through layers [34]. These methods

cause less bleeding, with respect to standard surgery, resulting in more accurate and precise outcome compared to the standard surgical technique [44].

Both approaches were used to treat HS affected patients with good outcomes, leading to lesion's healing, amelioration of skin texture, improved appearance of scars and rare recurrence of the disease; however, the post-operative skin recovery could take several weeks [34]. Surgical excision was commonly utilized to treat advanced active stages of the disease, instead vaporization should be preferred when the pathology presents with small stationary lesions with the possibility to spare some healthy skin areas from the total ablation [34]. In the last case the recovery was also more successful because the normal skin functioned as a reservoir for wound healing and tissue remodeling, moreover the scars were minor, and the tissue contraction reduced [44].

Secondary endpoint of this method is heat-mediated bacterial killing, with consequent lower infection rates after irradiation, and the cutting and sealing of the small blood and lymphatic vessels during the laser application [44]. Moreover, other important effects of CO_2 lasers are the radically removal of all keratinocytes in the lesions, ablation nodules, abscesses, and tunnels [34].

3.2. Intense pulsed lasers

The IPL utilizes flash lamps to create pulsed polychromatic high-intensity light that is absorbed by cellular chromophores. The subsequent transfer of photon energy to the chromophore structures leads to increased heat and target destruction. IPL is commonly used to remove hairs, since it acts on dark hairs follicles by destroying them through a thermal effect [41].

The rational use of IPL for treating HS is based on the fact that this pathology progresses from follicular occlusion leading to apocrine gland dysfunction [45]. Thus, the elimination of hair follicles could be advantageous for HS patients.

Some works reported a clinical improvement of HS condition in patients treated with IPL, specifically amelioration of Sartorius scores (a scoring system used in the clinical setting to diagnose HS and monitor the disease course [46]), decrement of recurrence, hair reduction, resolution of inflammation and pain [34]. These successful outcomes were obtained using laser devices with wavelengths set at 420 or 550 nm that, targeting melanin, can be employed to destroy pigmented hairs through photo-thermolysis. Only one study failed to find changes in patients' clinical condition using a 1064 Nd:YAG laser [47]: since over 1000 nm water absorption occurs in the tissue, with a

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consequent epidermal heating [41], it is possible that the excessive heating could negatively impact the improvement of patients' conditions.

3.3. Photodynamic therapy

PDT is a treatment that employs a photosensitizer and a light source (e.g. laser, IPL, light-emitting diodes). The most employed photosensitizing agents are the 5-aminolevulinic acid (ALA, an intermediate of the heme biosynthetic pathway) and its methyl ester 5-aminolevulinate (MAL) [48] . Inside cells these compounds are metabolized to the photo-active protoporphyrin IX [48] and activated by blue or red light, thus promoting the production of reactive oxygen species (ROS) [49] that oxidize the surrounding molecules causing damage and leading to cell death [42]. PDT has been widely used to treat inflammatory skin conditions[40] and different works reported its use for HS, despite with various outcomes, ranging from reduction of inflamed areas, severity indexes, as Sartorius score, and recurrence, to lack of clinical benefit [40,50,51].

The rationale for the use of PDT in HS is based on the selective destruction of cells within the lesions and the subsequent immune and inflammatory host responses [52,53]. Additionally, it has been suggested that the mechanism of action of PDT on HS could be also correlated to a greater absorption of photosensitizers in hair follicle and pilosebaceous glands compared to other tissues, with a consequent higher generation of ROS and follicle epithelium impairment [54,55].

However, the most important PDT effect is bacteria killing [56], based on that PDT is also able to disrupt bacterial biofilm [57]. The interaction between an altered immune response and microbial agents is at the basis of the bacterial opportunistic infections that could affect HS lesions leading to a well-known medical problem in HS [25,58–60]. Furthermore, some authors suggest that HS could be considered a immune-mediated inflammatory disorder in which however bacterial biofilm plays an important role [26]. So, PDT in this scenario is a particularly interesting remedy.

4. Photobiomodulation therapy

PBM works through chemical effects, thanks to the interaction between laser light and chromophores. However, beside the identification of the photoacceptor molecules, an additional, unresolved issue is the cell-signaling cascade activated by laser light. Increasing evidence tends to indicate that laser acts on the mitochondria[61]

augmenting adenosine triphosphate (ATP) production[62] , modulating the production of ROS, and activating transcription factors [63]. Changes in the cellular redox state regulate several transcription factors [64], including factor-1 dependent activator protein-1, nuclear factor kappa B, p53, activating transcription factor/cAMP-response element–binding protein, hypoxia-inducible factor-1 (HIF-1), and HIF-like factor. These molecules control the synthesis of proteins that ultimately increase proliferation and migration of different cell lines, regulating the levels of cytokines, growth factors and inflammatory mediators, thus fostering tissue oxygenation [65]. The mechanism is mediated via nitric oxide (NO) release: its potent vasodilator activity increases blood supply to laser irradiated tissues. Through this effect, PBM-mediated vascular regulation increases tissue oxygenation and subsequently allows for greater circulation of immune cells, which also contribute to the promotion of wound healing [66].

Accumulating experimental data indicate that tissue irradiation using a laser "optical window" of red and near infrared (NIR) wavelengths (600–1070 nm) results in an increased ATP synthesis: in this way, the electromagnetic energy of laser is transformed into cell energy [43]. The maximal tissue penetration could be reached in the red and infrared (IR) spectra, since the highest peaks of absorption of the principal tissue chromophores, hemoglobin and melanin, are below 600 nm. On the contrary, water absorbs in the IR wavelengths, while near blue wavelengths increase the scatter. Wavelengths in the range between 600 and 700 nm are mostly used to treat superficial tissues, whereas longer wavelengths in the range between 780 and 970 nm, which penetrate further, are used to treat deeper-seated tissues [67]. Nevertheless, the biological mechanisms that support the beneficial effects of PBM are still unclear.

The most important PBM biological effects are (figure 1): stimulation of wound healing, stimulation of angiogenesis/vasodilatation, anti-inflammatory effects, analgesic effect and antimicrobial effect; these effects are important to provide a rational application of PBM for the management of HS.

4.1. Stimulation of wound healing

The effects of PBM on wound healing are often attributed only to increased cell proliferation. Indeed, many studies report increased cellular proliferation of numerous cell types including fibroblasts, endothelial cells and keratinocytes[68]. However, the actual effect of laser light on cell proliferation is not completely understood, because of conflicting reports on the effects of PBM on different cell lines [69,70]. The physiological state of the cell at the moment of irradiation heavily influences the magnitude of the laser bio-stimulatory effect. This could explain why

the effect is not always detectable, not reproducible, as well as the uneven variability of the results reported in literature [71]. The effect of PBM is greater in cases of severe damage (e.g. trophic ulcers or difficult wounds), while the effect of laser light on normally regenerating wounds may be reduced. Moreover, the activation of lymphocytes and of the phagocytic activity of macrophages during the early stages of tissue repair, (approximately 6 hours after trauma) facilitates the cleaning of the wound and the establishment of the conditions needed for the subsequent proliferative phase[72]. Macrophages are the key cells responsible for the release of growth factors during the development of granulation tissue and along with granulocytes the phagocytosis process raises, leading to an activation of the immune-competent system (T- and B-lymphocytes), causing a specific immunologic defense. This is consistent with the improved defence-adaptation reaction and the faster elimination of the pathological process, often observed after PBM. Thanks to these processes the key phases of wound healing (transition from hematoma to fibroplasias, development of new blood vessels, production of collagen, and remodeling) could be successfully accelerated by PBM [72].

Karu[73] stated that light is able to increase cell proliferation, only if cells are weakly growing at the time of irradiation. Therefore, if a cell is totally efficient, laser irradiation is ineffective, so it will not be observed any therapeutic effect [74]. Fibroblasts are the key cells in the process of mucosal and skin wound healing: laser light specifically acts on those cells [75]. Its proliferative effect on this cell line is well established by many *in vitro* studies [76] on cultured human skin fibroblasts, accounting among the laser light effects an enhanced collagen production and an increased cell number. PBM set at low doses, around 2 J/cm^2, stimulates cell proliferation, while at doses higher than 16 J/cm^2 has suppressive effect. For this reason, the biological responses after PBM treatment are dose dependent[77]. Indeed, the way laser light interacts with biological tissues depends on the characteristics and setting of the employed device, mainly on wavelength and dose, but also on the optical properties of the treated tissue. Each clinical application should be carefully analyzed and scheduled before setting the PBM treatment to obtain the best results in terms of wound healing and patient's quality of life improvement.

4.2. Stimulation of angiogenesis/vasodilatation

PBM stimulates the proliferation of endothelial cells, resulting in the formation of numerous blood vessels, improved release of nutrients and oxygen, and increased production of granulation tissue[78]. It also promotes vascular smooth muscle relaxation, resulting in capillary vasodilatation, improves drainage liquid from the

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interstitial space, thus leading to pain relief due to the reduction of local edema. Indeed, the improved local microcirculation leads to a faster edema reabsorption and a quickening of the lymphatic drainage, promoted even by granulocyte diapedesis. The mechanism underling the effect of PBM on vasodilatation is the release of histamine, NO and serotonin. As result, a reduction of local ischemia and enhanced perfusion is achieved. PBM effect on vasodilatation increases the passage of nutrients and oxygen to the injured tissues, thus facilitating the repair and the removal of cellular fragments. PBM induced increases in NO, cytokines and growth factors are contributory to this process. Both blood and lymphatic vessels have been studied *in vivo* describing a significant increase and regeneration after PBM therapy. As circulation and perfusion accelerate and blood vessels diameters enlargement occurs, with a consequent increasing of circulating blood, patients assist to an accelerated tissue repair and healing processes [79].

4.3. Anti-inflammatory effects

PBM can improve mast cells degranulation: this effect results in an increased release of histamine, which leads to an acceleration of the inflammatory cascade. Since after PBM therapy this process develops more rapidly, the healing phase of tissues begins sooner improving the wound healing progression. Since inflammation entails both vascular and cellular events, at the local injured site, reactive components such as mast cells, bradykinins and prostaglandins are triggered. At the same time, the equilibrium of cellular membrane ions concentrations (Ca^{2+}, Na^+ and K^+), and the proton gradient over the mitochondria membrane, are positively activated by PBM. This mechanism is performed thanks to beneficial ROS production, which increases the concentrations of intracellular Ca^{2+} up taking in the mitochondria after PBM. PBM can create a shift in the cell redox potential generating greater oxidation, which leads to an increased ROS production and cell redox activity. Since the redox state regulates cellular signaling pathways, variation in the cellular redox state can activate or inhibit them. Due to these changes, several intracellular signaling pathways are activated, such as nucleic acid synthesis, protein synthesis, enzyme stimulation and cell cycle progression. Furthermore, changes in cellular redox state may also induce transcriptional changes, which lead to the regulation of several transcription factors [80].

4.4. Analgesic effect

PBM has been demonstrated to be efficacious to contrast different types of pain, from neuropathic[81] (characterized by the absence of a specific noxious stimulus triggered by lesions in the central or peripheral nervous system or chronic inflammation [82]) to orthodontic[83] and inflammatory pain in joints and lower back of the spine[84]. Systematic reviews of the literature show that wavelengths, energies, and time of treatment differ widely between the various studies examined, but currently a consensus on the efficacy of PBM has been established. The variability between the different studies could be due either to the nociception type, i.e. neuronal fibers activated by inflammatory pain differs from the ones activated in neuropathic pain, or to the anatomical location of the pain and thus to the nociception terminals distribution or proximity to skin surface.

Indeed, the detailed mechanism of action of PBM on sensory neurons is still elusive; the first site responsible for response could be the mitochondrial respiratory chain. In a model of primary rat dorsal ganglion neurons, PBM reduces mitochondrial membrane potential while blocking fast axonal transport and promoting varicosities formation [85]. Indeed, in another model using murine primary cortical neurons, PBM increases mitochondrial membrane potential, followed by augmented ROS production [86]. It is clear from these two examples that the cellular milieu profoundly influences the response to PBM, indicating the necessity of a deeper comprehension of the actors involved in laser response.

NO has been also identified as possible mediator of PBM analgesic effect; Shiva and Gladwin described a mechanism in which NO is liberated from intracellular stores (mainly mitochondria) after PBM stimulation, using near NIR wavelengths. Indeed, NO binds to cytochrome c oxidase (specifically the heme a3 in the active site of the enzyme) inhibiting mitochondrial respiration; after NIR light stimulation, NO is released from cytochrome c oxidase and metabolic rate in mitochondria can increase[87]. So, in this case, NIR light causes a double effect: increasing mitochondrial activity followed by neurotrophic effect mediated by NO.

Albert and co-workers in 2012 suggested another possible mechanism: the authors describe a "laser evoked neuronal voltage variation" (LEVV) in retinal ganglion cells. LEVV is an increase in membrane potential induced by IR light that reaches action potential level. In these neurons, IR light induces a train of action potentials mediated by opening of Transient Receptor Vanilloid channels 4. The authors suggest that activation of these channels can be due to local increase of temperature induced by IR light [88]. In this paradigm, IR light causes a train of action potential thus rendering the neuron unable to respond to other stimuli.

4.5. Antimicrobial effect

Despite the fact that systemic antibiotic therapy is often prescribed, it is estimated that in only 10% of HS patients they actually improve the clinical course of the disease[89] . Nevertheless, there is the concern for possible development of antibiotic resistance.

The emergent number of bacterial strains resistant to conventional antibiotics can affect the efficacy of medical therapy in HS, enhancing susceptibility towards infections, and increasing the onset of comorbidities correlated with altered microbial flora, for example pseudomembranous colitis and antibiotic-associated diarrhea [90].

It is well known since several years that laser irradiation is able to eliminate bacteria both *in vitr*o and *in vivo* conditions, using different wavelengths and sources of laser light in the range from 193 nm in the ultraviolet region, emitted by excimer lasers, to 10.6 μm in the far IR region, emitted by CO_2 lasers. It is usually believed that the bactericidal action of the laser is due to thermal heating. In fact, it is known that temperatures above 60°C can cause thermal damage and subsequent killing of bacteria. Grönqvist et al. demonstrated the antimicrobial effect of Nd:YAG laser (operating in the IR range) on *Staphylococcus epidermidis*, registering an agar temperature of approximately 70°C [91]. Schoop et al. have explored the antimicrobial effect of four laser systems that employ different wavelengths: 2940 nm (Er:YAG), 2780 nm (Er:YSGG), 1064 nm (Nd:YAG) and 810 nm (diode laser), obtaining significant reductions in *Escherichia coli* and *Enterococcus faecalis* viability [92]. Jawhara et al. conducted a study *in vitro* and *in vivo* on wound infections sustained by *Escherichia coli* using an 810 nm diode laser, showing that bacterial killing depends on laser fluence rather than power density. Interestingly, they obtained a complete killing of bacteria colonizing infected wounds registering a local temperature of 45°C, while bacteria heated without laser light resisted to temperature increase until 60°C. The authors hypothesize that chromophores inside bacteria, which may be sensitive to IR light, may cause a local intra-bacterial temperature increase, leading eventually to bacterial death [93].

Recently, the antimicrobial effect of blue light has been described in several research works, showing how the exposure to light in the range of 400-470 nm decreases viability in a heterogeneous group of bacteria, including *Pseudomonas aeruginosa*, *Porphyromonas gingivalis*, *Helicobacter pylori*, and methicillin-resistant *Staphylococcus aureus* [94,95]. The antimicrobial mechanism of blue light seems to rely exclusively on a photochemical effect, as the interaction of blue light with endogenous photosensitizing molecules, porphyrins and flavins is believed to provoke the ROS generation. Specifically, absorption of light brings porphyrin molecules into

an excited triplet state, leading to a non-radiative transfer of energy to the chemically stable molecular oxygen, which is also in a triplet ground state. The excited oxygen molecule dissociates into ROS (singlet oxygen ($^1O_2$), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), and possibly also hydroxyl radical ($\cdot OH$)), which damage the integrity of macromolecules such as lipids, DNA and proteins, leading eventually to microbial death [96].

Considering that irradiation parameters required to obtaining antimicrobial effects, in terms of irradiance and fluence, are lower than in the case of the photothermal effect, it seems that such approach may be used safely without provoking burn lesions on treated areas. In a recent study, Dai et al. performed an *in vivo* study using a 415 nm light emitting diode (LED) light applied on mouse burns infected with *Pseudomonas aeruginosa*. Histological analyses indicated no significant damage in the mouse skin exposed to blue light at the effective antimicrobial dose. In addition, survival analyses revealed that blue light significantly increased the survival rate of the infected mice [97]. While the majority of such studies have been performed using LED sources of light, there is growing evidence that blue lasers have the same antimicrobial efficacy[98,99]. The number of studies providing promising results is rapidly increasing and will lead to the performing of novel studies in clinical conditions in the near future.

5. Photobiomodulation as novel non-invasive tool to manage HS

HS is a debilitating, recurrent, skin disease that deeply affects patients' quality of life.

Nowadays treatment options range from short or long courses of antibiotics, anti-inflammatory and biologic drugs, to surgery.

HS patients are deeply affected by pain generated by skin lesions, considering that origins of aching can be either inflammatory or non-inflammatory; thus, strategies aimed at reducing general discomfort or pain were generally non-effective [28]. At present, in the most severe cases the combination of surgery and adalimumab is the first-choice option, being effective but invasive with long recuperation time and possible negative impact on patients' quality of life.

Different types of lasers have been used to treat HS affected patients, albeit with variable outcomes. However, most of them belong to the class of surgical lasers (such as the CO_2 laser and the pulsed lasers), whom employment can often lead to the development of scars or requires a photodynamic based approach.

Among the laser treatments, PBM at wavelengths of red and NIR, using low light irradiance and fluence rates, is an effective approach able to stimulate and foster cellular biological processes. PDT has already been widely

employed for different skin pathologies, such as wrinkles, acne or hypertrophic scars, and burns with good outcomes [100].

Moreover, we recently published a work based on the use of 970 nm laser light to stimulate wound healing in *NCSTN* KO keratinocytes (HaCaT) cells[101]. This model was used to mimic HS condition *in vitro* with the aim of unraveling the PBM effect on a simulation of surgical cut. We performed a scratch assay to monitor the cellular migration and the wound closure, therefore, cell metabolism, proliferation and cell cycle progression were assessed. We observed that PBM speeds up the wound closure, inducing cells' migration without affecting their proliferation, and exerts a potent action on metabolism of mutated keratinocytes, incrementing ATP production at 2-hours and cell metabolism after 24 hours. Our findings highlighted the potential effect of PBM in the context of HS, prompting future studies in this direction[101].

On the other hand, the laser therapy at the blue wavelength is another interesting application of laser light; it has been tested mostly *in vitro* and less *in vivo* on patients, although its anti-microbial effect is now widely recognized [102].

Although the combination of red-NIR and blue wavelengths has a rationale towards its employment in the treatment of HS, due to both pro-metabolic and anti-microbial effects, no studies have ever tested its efficacy yet. Indeed, PBM exerts promising and beneficial effects in promoting wound healing, inducing vasodilatation, reducing inflammation and pain [43]. Additionally, the employment of blue light could be interesting for the eradications of bacterial wound colonization [102], also acting on eukaryotic cells with proliferative effects [102]. As described above, two mechanisms are at the base of PBM activities: the absorption of light by cytochrome C oxidase, that could lead to the dissociation from NO with the mitochondrial respiratory chain stimulation, and the changing in the redox state with the production of ROS, that could activate different intracellular pathways [66,80,103].

Based on these biological effects and the non-invasive and painless nature of PBM, we hypothesize that HS patients could benefit from this treatment option. It may be recommended both during exacerbation phases and after surgery. [25,58–60]. PBM treatment sessions are very short and generally well-tolerated.

Also the economic impact should be taken into account, since after the laser acquisition, the formation of medical personnel deputed to PBM is relative simple, the patient can be treated in common outpatient clinic without anesthesia and part of the prescribed drugs could be eliminated or reduced. Based on the PBM characteristics and considering HS patients' discomfort, we believe that PBM could be an interesting therapeutic option, as third line

approach, for helping the management of HS. In particular, the employment of protocols that combine both red/NIR (bio-stimulatory) and blue (antimicrobial) wavelengths could achieve the maximum effectiveness of the treatment. For this reason, future works are needed aimed at disclosing the effect of PBM firstly *in vitro* (i.e. in patients' keratinocyte cells and in cell culture mimicking the disease) and then *in vivo*, employing HS animal models. All those research steps will be necessary in order to verify the rationale for PBM utilization and to test different laser protocols in order to optimize the outcome of the treatment.

We are aware that PBM could not completely eradicate HS, nevertheless, it could be a potential adjuvant third line treatment for the management of the pathology, particularly after skin surgery, together with other already known and widely used interventions.

Conflicts of Interest:

Ottaviani G. has a part-time employment in K-Laser d.o.o. (Sežana, Slovenia). The other authors have no conflict

of interest to declare.

Figure legends:

Figure 1. Schematic representation of photobiomodulation principal effects

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Photobiomodulation Therapy (PBM)

stimulation of wound healing and angiogenesis/ vasodilatation

anti-inflammatory effect

analgesic effect

anti-microbial effect

inflammation

pain

lesions

Hidradenitis Suppurativa (HS)

bacteria infections