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Role of phototherapy in the era of biologics

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Phototherapy is a safe and effective treatment for many dermatologic conditions. With the advent of novel biologics and small molecule inhibitors, it is important to critically evaluate the role of phototherapy in dermatology. Surveys have shown that many dermatology residency programs do not dedicate time to teaching residents how to prescribe or administer phototherapy. Limitations of phototherapy include access to a center, time required for treatments, and insurance approval. Home phototherapy, a viable option, is also underused. However, it should be emphasized that modern phototherapy has been in use for over 40 years, has an excellent safety profile, and does not require laboratory monitoring. It can be safely combined with many other treatment modalities, including biologics and small molecule inhibitors. In addition, phototherapy costs significantly less than these novel agents. Dermatologists are the only group of physicians who have the expertise and proper training to deliver this treatment modality to our patients. Therefore, to continue to deliver high-quality, cost-effective care, it is imperative that phototherapy be maintained as an integral part of the dermatology treatment armamentarium. (J Am Acad Dermatol 2021;84:479-85.)

Key words: biologics; broadband ultraviolet B; excimer; narrowband ultraviolet B; phototherapy; psoralen plus UVA; psoriasis; ultraviolet A1.

Ever since Goeckerman introduced the use of ultraviolet (UV) B (UVB) and tar in 1925,[1] phototherapy has been an integral part of dermatology training and expertise. Modern phototherapy has been in use for over 40 years.[2] This started with broadband UVB (BB-UVB) phototherapy and, in 1988, was replaced with the more effective narrowband UVB (NB-UVB) phototherapy. Psoralen and UVA (PUVA)—more accurately termed *photochemotherapy*—began in 1974.[3] Targeted phototherapy with an excimer laser or excimer lamp began in 1997.[4]

Exciting advances in the understanding of the molecular pathway and pathophysiology of dermatologic diseases have led to the development of many highly effective targeted therapies in psoriasis, atopic dermatitis, vitiligo, alopecia areata, and other dermatoses. These biologics and small molecule inhibitors have become an important part of dermatology practice, which raises the question on the role of phototherapy.

USE OF PHOTOTHERAPY

A 5-year report in 2002 showed that phototherapy use in the United States is declining. From 1993 to 1998, patient visits decreased by 85% for PUVA and by over 90% for phototherapy in general. Among the reasons cited for this decrease were the development of newer systemic agents, reluctance of patients to adhere to multiple weekly treatments, fear of UV-induced skin malignancies, and modifications in insurance coverage.[5] However, a 2018 study found that billing for phototherapy increased by 5% annually over a 15-year period (2000-2015). This

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study included Medicare beneficiaries only and did not account for patients with private insurance or those paying out of pocket; hence, it is likely that the actual number of patients receiving phototherapy is much higher. It should be noted that this increase was driven primarily by the use of excimer laser (25%-30% increase). In the same period, the use of UVB phototherapy and PUVA decreased by 3% to 6% and 9%, respectively.[6]

In other parts of the world, phototherapy use was higher than in the United States. In Australia, a nationwide survey of practicing dermatologists published in 2002 showed that 71% of respondents provided phototherapy, and among them, almost 90% had their own treatment facilities.[7] In France, the number of UV treatments administered annually increased by 12% from 2007 to 2010—nearly a decade after biologics were first introduced; however, follow-up data (2013-2016) saw a decline of the same by 15%, which was attributed to delays in initiation of biologic therapy.[8] Although clinical inertia was suggested as a reason for this delay,[8,9] it is also worthwhile to consider the fact that many guidelines do not endorse biologics as first-line agents, and a stepwise approach is still advocated.[10]

CAPSULE SUMMARY

- Novel and effective targeted therapies for dermatologic diseases raise questions regarding the role of phototherapy.
- Despite therapeutic advancements, phototherapy still has a role as a safe, well-established, cost-effective treatment option; only dermatologists have the expertise and training to make this treatment available to our patients.

PHOTOTHERAPY TRAINING AMONG DERMATOLOGY RESIDENTS

A 2017 study by Goyal et al[11] showed that there was a disparity between the demand for phototherapy and the time devoted to learning it during residency. Responses obtained from dermatology program directors across the United States showed that a majority (67%) regarded their phototherapy training as inadequate, which was primarily attributed to time deficiency.[11]

A cross-sectional survey[12] among US dermatology residents, published in 2015, showed that approximately 59% did not obtain any hands-on phototherapy training and that 42% had never observed phototherapy at all. Fewer than half of the residents felt that they could comfortably administer NB-UVB unsupervised, and fewer than 20% were comfortable with administering other modalities (excimer laser, PUVA, and BB-UVB).

Similarly, in 2015, Anderson et al[13] found that, among US dermatology residents, 29% and 76% were not comfortable with prescribing outpatient and home phototherapy, respectively. This discomfort stemmed from a lack of exposure and is significant because dermatology trainees who do not develop enough confidence to prescribe phototherapy during residency are less likely to do so in practice.

PHOTOTHERAPY AND BIOLOGICS

Efficacy data

Phototherapy primarily uses UV radiation. Depending on the pathogenesis of the disease being treated and the specific modality prescribed, phototherapy counteracts the pathologic changes that characterize inflammatory skin diseases through several key mechanisms: (1) induction of apoptosis, (2) modification of the cytokine milieu, and (3) immunosuppression.[14-16]

Phototherapy has been used successfully to treat many skin diseases. A partial list is shown in Table I. Among these, phototherapy for psoriasis has the most data. The different modalities that can be used for psoriasis are BB-UVB, NB-UVB, excimer light or laser, and PUVA (oral, topical, hand-foot soak, and bath/full-body soak).[17] BB-UVB is rarely used today and has largely been replaced by NB-UVB because of the latter's better efficacy.[18]

Oral PUVA has superior efficacy to NB-UVB for psoriasis. Treatment with NB-UVB can produce substantial improvement of moderate to severe psoriasis after approximately 20 to 36 treatments, whereas oral PUVA can generate equal or better results after a median of 16 to 17 sessions.[18] In a systematic review by Almutawa et al,[17] oral PUVA achieved the highest clearance rate (CR) (79%) but caused symptomatic erythema and blistering in 17% of patients. NB-UVB attained a 68% CR and was better tolerated (adverse effects in 7.8%), and bath PUVA was the least effective (58% CR) and least tolerated (adverse effects in 21%). Hence, although oral PUVA is more efficacious, better tolerability makes NB-UVB a preferred first-line phototherapy modality.[17] In practice, the high cost and intermittent availability of 8-methoxypsoralen in the United States, together with well-known, long-term adverse effects of photoaging and photocarcinogenesis, have further limited the use of PUVA.

Excimer laser or excimer light is a form of targeted UVB. It limits UV exposure to the involved areas only, making it ideal for localized disease (less than 10% body surface area) as well as difficult-to-treat

Abbreviations used:

BB-UVB: broadband ultraviolet B
CR: clearance rate
IL: interleukin
NB-UVB: narrowband ultraviolet B
PASI: Psoriasis Area and Severity Index
PUVA: psoralen and ultraviolet A
UV: ultraviolet
UVB: ultraviolet B

areas such as the scalp, palms, and soles.[4] It can produce results with as few as 8 treatment sessions compared to conventional NB-UVB, thereby reducing the cumulative UV dose.[4,18]

Outside the realm of psoriasis, NB-UVB is a first-line UV-based treatment option for many conditions including vitiligo, early mycosis fungoides, and atopic dermatitis. UVA1 penetrates deeper into the dermis and has shown benefit for sclerosing skin disorders such as morphea and scleroderma.[19] NB-UVB and UVA1 are also useful for therapeutic hardening of patients with polymorphous light eruption and solar urticaria, respectively.[20] For treatment-resistant dermatitis of the hands and feet, topical PUVA is frequently used. Oral PUVA is helpful for plaque stage mycosis fungoides, other forms of cutaneous lymphoma, and as a second-line UV-based treatment option for recalcitrant skin conditions that have failed or responded inadequately to NB-UVB.[21] The list of photoresponsive dermatoses is long, which underscores the versatility of this treatment modality.

Biologics are injected or infused monoclonal antibodies that block specific proinflammatory cytokines or receptors implicated in the pathophysiology of psoriasis and other inflammatory diseases.[16,22] These agents are grouped according to their cytokine target(s) as follows: tumor necrosis factor inhibitors (etanercept, infliximab, adalimumab, certolizumab), interleukin (IL) 12/IL-23 inhibitor (ustekinumab), IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), and IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab-rzaa).[22] A 2019 meta-analysis found risankizumab-rzaa to be the most efficacious biologic for psoriasis, followed by ixekizumab, guselkumab, and brodalumab.[23] Kim et al[24] noted that IL-17 inhibitors have the earliest onset of efficacy. The fastest, brodalumab, attained a 50% reduction in Psoriasis Area and Severity Index score (PASI) in less than 2 weeks and a 75% reduction in PASI in 4 weeks. The IL-17 inhibitors were also among the biologic agents that had the most sustained activity together with the IL-23 inhibitors and IL-12/23 inhibitor.

Table I. Common indications for phototherapy

Psoriasis
Vitiligo
Cutaneous T-cell lymphoma/mycosis fungoides
Polymorphous light eruption
Atopic dermatitis
Pruritus

A comparative study by Inzinger et al[25] showed that the efficacy rates of oral PUVA were comparable to those of infliximab and exceeded those of etanercept, efalizumab, alefacept, adalimumab, and ustekinumab. Additionally, a recent trial comparing patient-reported outcomes of NB-UVB versus adalimumab versus placebo showed that improvements in overall health-related quality of life scores were equivalent for both active interventions after 12 weeks.[26]

Safety and adverse effect profile

The acute adverse effects of phototherapy are relatively minor and include pruritus, tenderness, erythema, tanning, and blister formation.[18] For PUVA, the application or ingestion of a photosensitizer can incite skin phototoxicity, nausea, and/or vomiting.[18] The true risk of UV-induced skin cancer has long been a subject of debate and is a cause of hesitation for patients and providers alike. PUVA has been found to significantly increase the risk of squamous cell carcinoma in a dose-dependent manner, whereas the incidences of PUVA-induced melanoma and basal cell carcinoma are much lower.[14,27] NB-UVB and UVA1 have had no evidence of increased risk of photocarcinogenesis and are considered safe with proper supervision by most practitioners.[14,27,28]

These risks can be mitigated via thoughtful patient and modality selection, proper dosing and dose adjustment, protection of uninvolved areas, monitoring of cumulative UV dose, and periodic full-body skin examinations.[14] With the exception of PUVA, phototherapy does not require any pretreatment laboratory workup and can be safely administered to pediatric, elderly, and pregnant patients.

The adverse effects and safety of biologic medications should also be considered. With proper patient screening, biologics have shown good safety, particularly when compared to traditional systemic agents[24]; however, long-term data are scarce. Patients taking biologics have an increased risk of

infection because of the immunomodulatory effects of the medication. Tumor necrosis factor inhibitors have specifically been associated with an elevated risk of tuberculosis, hepatitis B, lymphoma, and other malignancies, whereas IL-17 inhibitors have been shown to induce and exacerbate inflammatory bowel disease and increase the risk for mucocutaneous candidiasis.[24,29] Depression and suicidality have been reported among patients taking brodalumab, although evidence on causation remains controversial.[24,29] Furthermore, parenteral administration of biologics makes injection site and infusion reactions a possibility.[24,29]

To minimize these risks, patients who are candidates for biologic therapy require workup before initiation and at regular intervals throughout treatment. Laboratory tests consisting of a complete blood count, liver function test, hepatitis panel, and tuberculosis screening are regularly performed.[22,30] Additional tests may be warranted depending on patient-specific or medication-specific risk factors. Recent guidelines suggest that certain biologic agents may be safely administered to pregnant, lactating, and pediatric patients; however, information regarding this is still limited.[22,31]

The COVID-19 pandemic raised numerous questions regarding biologics' safety that lack clear, evidence-based answers. Based on experience with HIV-positive patients, and in keeping with the practice of social distancing, home phototherapy is a reasonable option during this pandemic.

Cost

The price of treatment is a reality that must be considered when formulating a management plan; and for chronic skin conditions, this may entail lifelong expenditures. According to a study in Scotland, the average price for a course of NB-UVB is £257, whereas topical medications cost £128 annually per patient. Implementing NB-UVB resulted in a 40% reduction in cost (£50.74 per patient annually) due to less need for medications.[32]

A 2010 analysis estimated that biologics cost at least twice as much as NB-UVB and PUVA combined. The least expensive biologic included in the study, adalimumab, was quoted at $23,538 for the first year of therapy alone, compared to $3148 and $7582 for a year of NB-UVB and PUVA, respectively.[33] Six years later, the price of adalimumab increased by more than 2-fold ($58,045) for the first year of therapy alone.[34]

Home phototherapy units cost anywhere between $2500 and $5000.[35,36] They can offset the indirect expenses incurred from office-based treatment (transportation, lost income from work absences, inconvenience), but a disadvantage is that patients must pay for the device up front because few insurance policies offer coverage. A comparative study showed that although in-office phototherapy was less costly at the beginning of treatment, it became 5 times more expensive than home phototherapy after 3 months.[36] Additionally, when compared to biologics, home phototherapy cost up to 36 times less over a 3-year period.[37]

Biologics have remarkable efficacy and a good safety record to date, and they are convenient to administer. This may provide rationale for physicians and patients to justify the high cost, especially when factoring in the intangible phototherapy expenses. However, some patients may respond inadequately to biologic therapy and require dose escalation or more frequent administration, thereby further increasing the cost of treatment.[34]

COMBINATION THERAPIES

In practice, treatments are often combined to enhance efficacy when rapid suppression of disease activity is desired or when monotherapy is insufficient to achieve and maintain control. Several reviews and guidelines on psoriasis treatment have reported on the combination of phototherapy with various topical drugs, traditional systemic agents, and biologics.[14,16,38,39] With each medication having its own adverse effects, enhanced toxicity from combining 2 or more modalities is a possibility. Contrarily, some combinations of medications may lower the chances of long-term adverse effects by reducing the cumulative dose of either modality alone or have minimal to no additive toxicity because of the relatively short duration of adjunctive treatment.[38]

The concomitant administration of acitretin with NB-UVB has been found to hasten clinical response, reduce the required acitretin dose, and decrease the number of phototherapy sessions by approximately 20%, thereby lowering the cumulative UV dose and theoretical risk for photocarcinogenesis.[14,38,40] Similar effects have been observed with acitretin plus PUVA, and given the established skin cancer risk with this modality, the coadministration of an oral retinoid is particularly valuable.[40-43] Because retinoids have a keratolytic effect, phototherapy dose escalations must be proceeded with cautiously when using this combination.[14] Most protocols recommend UV dose reduction by 33%.

Several studies have shown that NB-UVB in conjunction with biologics is safe, synergistic, and well tolerated, although long-term data on these combinations have not been explored. Patients with moderate to severe psoriasis who complied with

Table II. Summary of advantages and limitations of phototherapy and biologics

	Phototherapy	Biologics
Advantages	Effective	Highly effective (takes 8-12 weeks)
	Rapid acting (targeted phototherapy)	Immune modulators
	Known long-term safety record	Good short-term safety record
	No laboratory monitoring needed	Convenient to administer
	Safe for children and pregnant and nursing mothers (NB-UVB)	
	Lower cost	
Limitations	Availability and access	Expensive cost
	Necessitates equipment, staff, and space	Requires laboratory testing and monitoring
	Requires patient's time and effort	Lacking long-term safety data
	Involves thorough patient education (for home phototherapy)	

thrice-weekly NB-UVB in addition to etanercept showed biopsy-proven improvement without additional adverse effects compared to etanercept alone.[38,44] Moreover, a half-body comparison of adalimumab plus NB-UVB versus adalimumab alone yielded a 33% greater PASI reduction on the irradiated body half compared to the nonirradiated half.[45] Analogous results were obtained in a similar trial on ustekinumab.[46] Erythema was the most common adverse effect.[45,46] To date, there are no studies on the combination of PUVA with any biologic.[41]

LIMITATIONS OF PHOTOTHERAPY

One major challenge concerning adherence to phototherapy is limited access. In the United States, phototherapy facilities are concentrated in urban areas of the East and West Coasts and the Midwest region east of Mississippi, leaving 89% of counties without a treatment center.[6] This misdistribution appears to reflect the geographic location of dermatology providers in general and not the underuse of phototherapy per se. Nonetheless, the indirect costs of travel and lost income from missing work can discourage patients from complying with repeated phototherapy treatments.[6] Other limiting factors are the resources needed to establish a phototherapy center (equipment, space, trained staff) and the need for prior authorization.

Home phototherapy devices can potentially address these hurdles. Several randomized trials have shown that home-based and office-based phototherapy are equally safe and effective, with higher satisfaction and adherence in favor of home phototherapy; however, this also entails higher up-front costs for the patient and the need for a provider who is sufficiently familiar with home phototherapy.[47] In addition, phototherapy has possible long-term risks. Therefore, in practice, it is usually administered intermittently, and patients may experience disease relapses within weeks to months of discontinuation. Combining phototherapy with other modalities can not only decrease the likelihood or severity of a relapse but also lower the risk of adverse effects from either modality alone. With proper patient education, home-based phototherapy is another option.

The advantages and limitations of phototherapy and biologics are summarized in Table II.

CONCLUSION

Phototherapy remains an indispensable treatment option for many cutaneous diseases. Its versatility, cost effectiveness, and unparalleled safety makes it a viable first-line treatment or adjunct when other treatment regimens fall short. Just as there are numerous indications for phototherapy alone, there are a wide variety of modalities with which it can be combined. As dermatologic management becomes more individualized and costly, improved access to this treatment modality through expanding residency training curricula and prescribing of home devices will prove that even in the era of biologics, phototherapy will stand the test of time. Dermatologists are the only group of physicians who have the knowledge and expertise to supervise the delivery of phototherapy. Therefore, it is essential that we as a specialty continue to make sure this treatment option is available to our patients.

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