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EVIDENCE-BASED REVIEW ARTICLE

Systematic Review of UV-Based Therapy for Psoriasis

Fahad Almutawa · Naif Alnomair · Yun Wang · Iltefat Hamzavi · Henry W. Lim

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Abstract

Background UV-based therapies, which include narrow-band (NB) UVB, broad-band (BB) UVB, and psoralen and UVA (PUVA), are well known treatment options for moderate to severe plaque psoriasis. However, there are limited evidence-based reviews on their efficacy, short-term safety, and tolerability.

Aim The aim of the study was to evaluate the efficacy, short-term safety, and tolerability of UV-based therapy in the treatment of adults with moderate to severe plaque psoriasis.

Methods We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating NB-UVB, BB-UVB, and PUVA in adults with moderate to severe plaque-type psoriasis. Our efficacy outcomes were ≥ Psoriasis Area and Severity Index (PASI)-75 and clearance. We evaluated the short-term safety and tolerability from the percentage of adverse effects and withdrawal due to adverse effects, respectively.

Results Forty-one RCTs, with a total of 2,416 patients, met the eligibility criteria and were included in the analysis. In regard to PASI-75 in monotherapy trials, PUVA (mean: 73 %, 95 % CI 56–88) was the most effective modality. Trials with BB-UVB also showed a high PASI-75 (73 %) but with a wide CI (18–98) due to heterogeneity of the total available three studies. This was followed by NB-UVB (mean: 62 %, 95 % CI 45–79) then bath PUVA (mean: 47 %, 95 % CI 30–65). In regard to clearance in the monotherapy trials, PUVA (mean: 79 %, 95 % CI 69–88) was superior to NB-UVB (mean: 68 %, 95 % CI 57–78), BB-UVB (mean: 59 %, 95 % CI 44–72), and bath PUVA (mean: 58 %, 95 % CI 44–72). The percentages of asymptomatic erythema development in monotherapy trials were 64 % for BB-UVB, 57 % for NB-UVB, 45 % for PUVA, and 34 % for bath PUVA. Symptomatic erythema or blistering percentages for the monotherapy trials were as follows: 7.8 % for NB-UVB, 2 % for BB-UVB, 17 % for PUVA, and 21 % for bath PUVA. The percentages of withdrawal due to adverse effects were 2 % for NB-UVB, 4.6 % for BB-UVB, 5 % for PUVA, and 0.7 % for bath PUVA monotherapy trials.

Conclusions As a monotherapy, PUVA was more effective than NB-UVB, and NB-UVB was more effective than BB-UVB and bath PUVA in the treatment of adults with moderate to severe plaque-type psoriasis, based on clearance as an end point. Based on PASI-75, the results were similar except for BB-UVB, which showed a high mean PASI-75 (73 %) that was similar to PUVA, but with a wide CI (18–98). The short-term adverse effects were mild as shown by the low rate of withdrawal due to adverse effects.

F. Almutawa
Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait

N. Alnomair
Department of Dermatology, Mount Sinai School of Medicine, New York, NY, USA

Y. Wang
Department of Public Health Science, Henry Ford Hospital, Detroit, MI, USA

I. Hamzavi · H. W. Lim (✉)
Department of Dermatology, Henry Ford Medical Center-New Center One, 3031 West Grand Blvd Suite 800, Detroit, MI 48202, USA
e-mail: hlim1@hfhs.org

1 Introduction

Psoriasis is a chronic inflammatory disease that affects the skin and/or the joints. The prevalence of psoriasis worldwide ranges from 0.6 to 4.8 % of the general population [3]. In the USA, based on data collected in 2003–2004, the prevalence is 3.15 %, which corresponds to approximately 5 million adults between the ages of 20–59 years. [3] The disease can be associated with adverse physical and mental effects that are comparable to those in patients with internal malignancies, heart diseases, diabetes mellitus, and depression [4]. Psoriasis is also associated with an increase in the prevalence of metabolic syndrome, especially abdominal obesity, hypertriglyceridemia, and low levels of high-density lipoprotein [5]. This increase in prevalence was shown to be higher with increasing severity [6]. Clinically, psoriasis is classified into major phenotypes, which are plaque, guttate, pustular, and erythrodermic [7].

Plaque psoriasis is the most common subtype and accounts for approximately 90 % of psoriasis patients [7]. Most of the cases are mild and can be controlled with topical medications. However, in approximately 17 % of patients, the disease is moderate to severe [3]; for these patients, additional therapeutic options include UV-based therapy [UVB phototherapy or psoralen and UVA (PUVA) photochemotherapy], systemic therapy (methotrexate, cyclosporine, mycophenolate mofetil, oral retinoids), or biologics.

According to the American Academy of Dermatology guidelines for the treatment of psoriasis, the first line of treatment of psoriasis involving more than 5 % of the body surface area in both sexes is UVB phototherapy [broadband (BB) or narrow-band (NB)], either alone or in combination with oral retinoid or methotrexate [8]. Also, the National Psoriasis Foundation has recommended UVB phototherapy to be tried before systemic and biologic agents in moderate to severe psoriasis [9]. These recommendations are based on the long-term efficacy and safety of phototherapy in the treatment of psoriasis.

At present, with the rapidly increasing options for the treatment of psoriasis, UV-based therapy is still an important therapeutic modality, both as monotherapy and in combination with other treatments. The mechanisms of action of UV-based therapy in psoriasis include local immunosuppression through the effect on Langerhans cells, cytokines, and adhesion molecules, inhibition of proliferation of keratinocytes and angiogenesis, and induction of T-cell apoptosis [8].

Psoriasis Area and Severity Index (PASI) score, which is the most studied and validated score to assess the severity of psoriasis, was shown in a recent systematic review to be the best outcome measure in assessing the severity of plaque psoriasis [10]. PASI-75, which is the percentage of patients that achieved a 75 % reduction in their baseline PASI, is now becoming the standard in determining the efficacy of a given therapy. PASI-75 has been used in systematic reviews that compare different systemic and biologic treatments of psoriasis [11–14].

Clearance is another important end point from the perspective of both the patient and the physician. It has been used frequently in older studies assessing the efficacy of PUVA treatments. In 1978, the more detailed scoring system, PASI, was introduced and since then, it has been widely used [15]. However, even after the development of PASI, clearance continued to be used as an outcome measure in some studies on UV-based therapy.

The aim of this systematic review is to assess the efficacy, short-term safety, and tolerability of NB-UVB, BB-UVB, and PUVA, both as monotherapy and as part of combination therapy with topical and systemic treatments, including biologics, for the treatment of widespread moderate to severe plaque psoriasis.

2 Methods

We searched MEDLINE, EMBASE, and Cochrane databases. Our keywords were ‘psoriasis’ in combination with ‘phototherapy’, ‘photochemotherapy’, ‘UVB’, ‘BB-UVB’, ‘broadband UVB’, ‘NB-UVB’, ‘narrowband UVB’, ‘ReUVB’, ‘PUVA’, ‘RePUVA’, and ‘D-PUVA’ (i.e., topical vitamin D derivatives combined with PUVA). The search was limited to randomized clinical trials, humans, English language, and publication years from 1980 to 2011. We included only randomized controlled trials (RCTs) of parallel groups and bilateral right to left comparisons. The participants were patients older than 16 years with widespread plaque psoriasis. We excluded other types of psoriasis, such as guttate, pustular, and erythrodermic. We also excluded inpatient studies and studies shorter than 4 weeks’ duration. Targeted phototherapy, photodynamic therapy, and topical PUVA were excluded because their efficacy can not be compared with generalized UV-based therapy. We excluded studies that evaluated the efficacy of treatments on selected lesions or part of the body (instead of full or half body), since these are often milder cases for which the studies usually did not use PASI score to measure response.

Our main outcome was the percentage of patients that achieved PASI-75 or above, and the percentage of patients that achieved clearance. In trials reporting PASI-80 or PASI-90, they were grouped with PASI-75 and above. In trials reporting PASI before and after, but not PASI-75, we calculated PASI-75 by assuming normal distribution of the PASI changes. Under clearance, we included only trials that reported complete clearance, clearance with minimal

residual activity, or ≥90 % improvement from the baseline.

The safety of the interventions was assessed by the percentage of acute adverse effects. We divided the adverse effects for UVB into asymptomatic erythema and symptomatic erythema or blistering. For PUVA, the adverse effects were divided into asymptomatic erythema, symptomatic erythema or blistering, and nausea/vomiting. The tolerability was assessed by the percentage of withdrawals due to adverse effects.

Two of the authors (F.A. and N.A.) determined study eligibility and abstracted data that included sample size, intervention, starting dose, increments, frequency, baseline PASI, PASI at the end of the study, PASI-75 or above, clearance, adverse effects, and withdrawal due to adverse effects. We assessed methodological quality according to the Jadad scoring system, which is a 0–5 score from the lowest to highest quality. The Jadad scoring system has been used in many systematic reviews, and is based on five questions, with the positive answer to each question assigned 1 point. The questions are (1) was the study randomized, (2) was the study double blinded, (3) was there a description of the withdrawal, (4) was the randomization process described and valid, and (5) was the double-blinding process described and valid? [16].

3 Data Analysis

PASI-75 was estimated by assuming normal distribution of PASI change for studies that did not report PASI-75 response, but reported baseline and end of study PASI. For the purpose of the meta-analysis, a random effects model proposed by DerSimonian and Laird was applied to calculate the pooled effect size [61]. For proportion outcomes, the Freeman-Tukey variant of the arcsine square root transformation [17] was used for transforming proportion into quantities, and back-transformation was utilized to have final weighted pooled proportion [18].

4 Results

A total of 41 RCTs with a total of 2,416 patients investigating NB-UVB, BB-UVB, and PUVA for the treatment of widespread plaque-type psoriasis met the inclusion criteria (Fig. 1). Tables 1, 2, 3, 4, 5, 6 and 7 include the details of these studies.

RCTs evaluating NB-UVB, BB-UVB, and PUVA were divided into studies that have clearance or PASI-75 and above as an endpoint. We calculated the estimated PASI-75 by assuming normal distribution of PASI changes for RCTs that did not provide PASI-75.

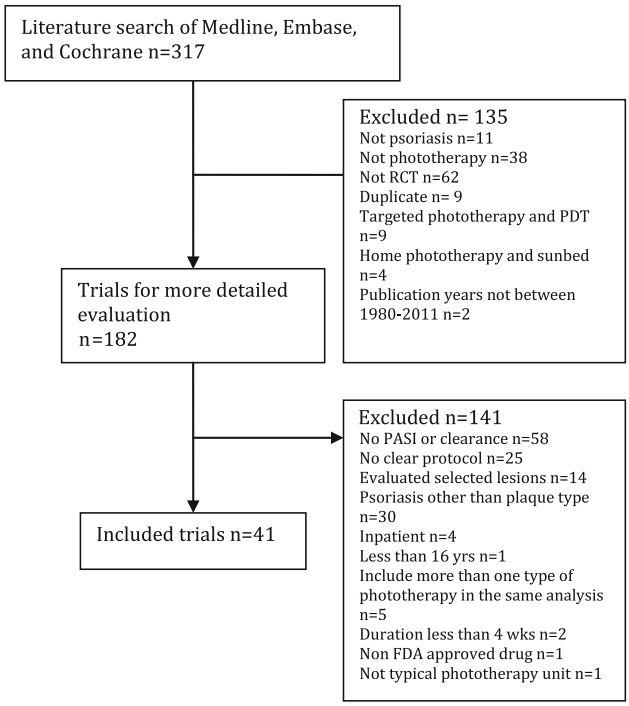

Fig. 1 Flow chart of the searched trials. *PASI* Psoriasis Area and Severity Index, *PDT* photodynamic therapy, *RCT* randomized controlled trials

4.1 Narrow-Band UVB

4.1.1 Mean Percentage of Patients Achieving Psoriasis Area and Severity Index (PASI)-75

The mean PASI-75 as calculated from nine RCTs with 293 patients for NB-UVB monotherapy was 62 % (95 % CI 45–79) (Fig. 2) [19–27]. The duration of these studies ranged from 4 to 24 weeks. The total number of treatments ranged from 14 to 34. The most common treatment frequency found in all studies was three treatments per week, ranging from two to five per week. The initial dose is either according to skin type or minimal erythema dose (MED). Five of the nine studies used the patients' MED as the basis of the starting dose [19, 24, 26, 27], with patients in three of the studies started with 70 % of the MED [19, 24, 27], one study 50 % [26], and another 35 % [24]. With regard to increments, 20 % was used in 7 of the 9 studies [19, 22–27]. Forty percent increments were used in one study [24], and a fixed increment in another (Table 1) [21].

There were two studies that investigated the combination of NB-UVB with topical treatments (Table 2) [20, 21]. The percentage of patients achieving estimated PASI-75 for the trial combining NB-UVB and calcipotriol was 52 % (95 % CI 32–71) [21], and for the trial combining NB-UVB and tazarotene, 10 % (95 % CI 0–28) [20]. In these two studies, the authors did not report PASI-75; therefore,

Table 1 Trials with NB-UVB monotherapy

Trial	No. of participants	Starting dose	Dose increments	Dose frequency (per week)	Mean no. of treatments [mean ± SD, or mean (range)]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD, or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[f] [16]
Dawe et al. [35][a]	21	70 % of MED	20 %	3	17			76		3
		70 % of MED	20 %	5	23.5			76		
Brands et al. [21]	28	Skin type[b]	2 1/3	3	31.7	12.5 (3.4–35.1)	3.1 (0.7–24)		50[d]	3
Gordon et al. [36]	51	70 % of MED	30–40 % weekly	2	25.3			63		3
Behrens et al. [20][a]	10	Skin type[b]	Not available	5	14 (13–17)	18.3 (15.01–20.50)	9.5 (7.7–11.7)		0[d]	1
Cameron et al. [33]	58	70 % of MED	20 %	2	24.4 (11–41)			69		3
	55	70 % of MED	20 %	3	23 (14–38)			80		
Rim et al. [38]	18	70 % of MED	50 mJ	3	43.3 ± 13.9	17.6 ± 12.1		61.1		2
Dawe et al. [34][a]	28	70 % of MED	20 %	3	24.5			75		3
Markham et al. [37]	24	70 % of MED	20 %	3	25.5 (18–32.5)	13.9 (12.2–17.5)		100		2
Snellman et al. [26][a]	17	50 % of MED	20–30 %	3	30 (22–30)	8.5 (1.8–15.2)	1.0 (0–6.6)	30	59	3
Asawanonda and Nateetongrungsak [19]	13	70 % of MED	20 %	3		14.61 ± 7.23	4.62 ± 3.57		45[d]	5
Yones et al. [27]	45	70 % of MED	20 %	2	28.5	10.6 (8.0–27.9)	2.3 (0–21.5)	51	52[d]	5
Kirke et al. [1]	50	MED	40 % on alternate treatment	3	28.4	7.5 (2.1–27.9)		56		3
Bagel [32][a]	12	Skin type[b]	10 %	3				50		2
Kleinpenning et al. [24]	55	70 % of MED	40 %	3	20.6 ± 6.9				75[e]	3
	54	35 % of MED	20 %	3	24.1 ± 6.1				67[e]	

Table 1 continued

Trial	No. of participants	Starting dose	Dose increments	Dose frequency (per week)	Mean no. of treatments [mean ± SD, or mean (range)]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD, or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[f] [16]
Mahajan et al. [25]	20	Skin type[b]	20 %	3	34.05 ± 16.92	14.4 ± 2.8			70	3
Dayal et al. [23]	30	Skin type[b]	20 %	2	16.4 ± 4.13	16.82 ± 3.9	1.6 ± 1.2		100	3
Chauhan et al. [22]	21	Skin type[b]	20 %	3	29.6 ± 9.8	15.8 ± 2.9			81	2

MED minimal erythema dose, *NB-UVB* narrow-band UVB, *result PASI* PASI at the end of the study

[a] Within patient comparison trial

[b] Skin type: starting dose is based on the Fitzpatrick skin type

[c] PASI: Psoriasis Area and Severity Index

[d] Estimated PASI-75

[e] PASI-90

[f] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

we calculated PASI-75 assuming normal distribution on the PASI changes, which could underestimate the PASI-75. However, it is clear that these two studies did not show additional advantage of combination therapy with calcipotriol or tazarotene over NB-UVB monotherapy.

Six trials that combine NB-UVB with systemic or biologic treatments were included (Table 2) [19, 25, 28–31]. In one trial that evaluated the combination of NB-UVB with acitretin, only 56 % of the 30 patients achieved PASI-75 [30] which is close to the PASI-75 of NB-UVB alone (62 %). However, combining NB-UVB with methotrexate was very efficacious with an average of 94 % (95 % CI 81–100) of 31 patients from two trials achieving PASI-75 or above [19, 25].

The addition of biologics was also very efficacious. When adalimumab was added to NB-UVB, all four patients achieved PASI-75 [31]; when alefacept was added, an average of 97 % (95 % CI 85–100) of 35 patients from two trials achieved PASI-75 [28, 29].

4.1.2 Mean Percentage of Patients Achieving Clearance

The mean clearance rate of NB-UVB monotherapy from ten trials with 379 patients was 68 % (95 % CI 57–78) (Fig. 3), which was close to the result of trials that have PASI-75 as an endpoint (62 %) [1, 26, 27, 32–38].

Clearance was achieved in 90 % (95 % CI 71–100) of ten patients treated with NB-UVB and calcipotriol ointment with an average of 43 treatments [38]. When liquor carbonis detergens (LCD, coal tar solution) was combined with NB-UVB, 58 % (95 % CI 30–86) of 12 patients achieved clearance [32], which is not better than the clearance rate of NB-UVB alone (68 %) (Table 2) [1, 26, 27, 32–38].

The combination of 8-methoxypsoralen (8-MOP) with NB-UVB was evaluated in 72 patients from two trials with an average clearance rate of 84 % (95 % CI 74–92) [39, 40]. One trial combined bath PUVA with NB-UVB; this resulted in clearance in 92 % (95 % CI 77–100) of the 12 patients (Table 2) [41].

4.2 Broad-Band UVB

4.2.1 Mean Percentage of Patients Achieving PASI-75

The mean PASI-75 of BB-UVB monotherapy from three trials with 246 patients is 73 % (95 % CI 18–98) (Fig. 2) [2, 42, 43]. Addition of a saline bath before BB-UVB in one study resulted in 39 % (95 % CI 28–50) of patients achieving PASI-75, offering no advantage in efficacy compared with monotherapy [42]. On the other hand, one study combining calcipotriol cream with BB-UVB resulted in 76 % (95 % CI 67–85) of the 84 patients reaching PASI-75 or more (Table 4) [2].

Table 2 Trials with NB-UVB/combination

Trial	No. of participants	Intervention	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD, or mean (range)]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD, or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[e] [16]
Calzavara-Pinton [41][a]	12	NB-UVB + PUVA (bath)	70 % of MED	40 %	4	13 ± 3.46	13.18 ± 3.49	0.47 ± 1.04	92	78[f]	1
Brands et al. [21]	25	NB-UVB + calcipotriol	Skin type[b]	2 1/3	3	31	13.2 (3.5–27.3)	3.0 (0.7–19.2)		52[f]	3
Rim et al. [38]	10	NB-UVB + calcipotriol	70 % of MED	50 mJ	3	43.1 ± 13.4	16.3 ± 5.1		90		2
Behrens et al. [20][a]	10	NB-UVB + tazarotene	Skin type[b]	Not available	5	14 (13–17)	18.3 (15.01–20.50)	6.5 (5.29–7.91)		10[f]	1
Bagel [32][a]	12	NB-UVB + LCD	Skin type[b]	10 %	3				58		2
De Berker et al. [39]	50	NB-UVB + psoralen	Skin type[b]	10 % weekly	2	15			86		3
Khurshid et al. [40]	22	NB-UVB + psoralen	Skin type[b]	0.1–1 J/cm^2	3	16			77.3		1
Ozdemir et al. [30]	30	NB-UVB + acitretin	70 % of MED	10–20 %	3	20.7 ± 5.1	15.5 (11.2–33)	3.9 (1.3–17.4)		56	3
Asawanonda and Nateetongrungsak [19]	11	NB-UVB + methotrexate	70 % of MED	20 %	3		18.05 ± 10.39	0.31 ± 0.44		90[d]	5
Mahajan et al. [25]	20	NB-UVB + methotrexate	Skin type[b]	20 %	3	17.05 ± 6.71	16.02 ± 3.51			95	3
Ortonne et al. [29]	10	NB-UVB + alefacept (6 weeks)	70 % of MED	15 %	3		29.5 (15.6–44)			100	2
	11	NB-UVB + alefacept (12 weeks)	70 % of MED	15 %	3		27 (13.5–47.4)			100	2
Legat et al. [28][a]	14	NB-UVB + alefacept	50 % of MED	Depending on the erythema	3	21			43	86	2
Wolf et al. [31][a]	4	NB-UVB + adalimumab	70 % of MED	100 mJ/cm^2	3		14.8	2		100	2

LCD liquor carbonis detergens (coal tar), *MED* minimal erythema dose, *NB-UVB* narrow-band UVB, *PUVA* psoralen and UVA, *result PASI* PASI at the end of the study

[a] Within patient comparison trial

[b] Skin type: starting dose is based on the Fitzpatrick skin type

[c] PASI: Psoriasis Area and Severity Index

[d] PASI-90

[e] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

[f] Estimated PASI-75

Table 3 Trials with BB-UVB monotherapy

Trial	No. of participants	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[b] [mean ± SD, or mean (range)]	Result PASI[b] [mean ± SD]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[d] [16]
Menkes et al. [45]	19	100 % of MED	50 % then 40, 30, 20, 19, 18, 17, 16, 15 %	3	21			74		2
Dover et al. [44]	29	80 % of MED	20 %	3	31.8 ± 5.5			59		4
Ramsay et al. [2]	80	Based on MED	25 %	3	25	11.7 ± 4.5		65	73.4[c]	3
Brockow et al. [42]	64	50 % of MED	25 % up to 10 Rx then 10 %	3	18	18 (12–23)			23	3
Kirke et al. [1]	50	MED	40 % on alternate Rx	3	30.4	6.1 (2.7–21.7)		40		3
Valkova [43]	102	Skin type[a]	20 J/cm^2 every other Rx	3	15.9 ± 0.4	8.9 ± 0.3	1.1 ± 0.1		100[e]	2

BB-UVB broad-band UVB, *MED* minimal erythema dose, *Rx* treatment, *result PASI* PASI at the end of the study

[a] Skin type: starting dose is based on the Fitzpatrick skin type

[b] PASI: Psoriasis Area and Severity Index

[c] PASI-80

[d] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

[e] Estimated PASI-75

Table 4 Trials with BB-UVB/combination

Trial	No. of participants	Intervention	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[f] [16]
Menkes et al. [46]	30	BB-UVB + tar oil	50 %	50 %	3	17			63		2
Dover et al. [45]	24	BB-UVB + fluocinonide	80 %	20 %	3	30.2 ± 4.6			54		4
Kragballe [47][a]	20	BB-UVB + calcipotriol	50 %	Suberythemogenic	3				39		2
Molin et al. [48] series A[a]	98	BB-UVB + calcipotriol	70 %	40 %	3		10	1.6	57		2
Ramsay et al. [2]	84	BB-UVB + calcipotriol	Based on MED	15 %	2	22	11.6 ± 4.9		60	76.2[d]	3
Brockow et al. [43]	79	BB-UVB + saline bath	50 %	25 % up to 10 Rx then 10 %	3	18	17 (12–24)			39	3
Valkova [44]	91	BB-UVB + bergamot oil	Skin type[b]	20 J/cm^2 every other Rx	3	14.8 ± 0.7	10.3 ± 0.7	0.8 ± 0.2		100[e]	2
Ortonne et al. [30]	9	BB-UVB + alefacept (6 wks)	50 %	Based on skin type[b]	3		9.9 (5.2–24.9)			42 (approximately)	2
	10	BB-UVB + alefacept (12 wks)	50 %	Based on skin type[b]	3		6.4 (4.6–13.5)			57 (approximately)	2

BB-UVB broad-band UVB, *MED* minimal erythema dose, *Rx* treatment, *result PASI* PASI at the end of the study

[a] Within patient comparison trial

[b] Skin type: starting dose is based on the Fitzpatrick skin type

[c] PASI: Psoriasis Area and Severity Index

[d] PASI-80

[e] Estimated PASI-75

[f] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

Table 5 Trials with PUVA monotherapy

Trial	No. of participants	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD, or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[e] [16]
Lauharanta et al. [50]	20	1–1.5 J/cm^2		3	26.5			20	95	2
Saurat et al. [55]	22	Skin type[b]	0.5 J/cm^2	3	19.9			80		3
Collins and Rogers [48]	22	Skin type[b]	0.5–1 J/cm^2 every 3rd Rx	3	14.8 ± 3.9			64	73	3
Collins et al. [53][a]	37	70 % MPD	40 %	2	9.5			94		3
		Skin type[b]	0.5–1 J/cm^2	2	13			91		
De Berker et al. [39]	50	2.5 J/cm^2	40 % weekly	2	16.5			74		3
Gordon et al. [36]	51	Skin type[b]	40 % decrease to 10 %	2	16.7			84		3
Kirby et al. [54]	40	Skin type[b]	40 % weekly	2	16	14		95		2
	40	50 % MPD	40, 30, 25, 20, 15, 10 then 5 %	2	14	15		68		
Khurshid et al. [40]	22	Skin type[b]	0.1–1 J/cm^2	3				86		1
Markham et al. [37]	25	70 % MPD	20 %	2	19	15.2 (10.8–18.9)		84		2
Torras et al. [52]	60	Skin type[b]	0.5 J/cm^2 every 2 Rx	3	25.2 ± 5.8	18.09 (16.62–19.56)	7.03 (5.56–8.5)		47.3	3
Yones et al. [27]	43	70 % MPD	20 %	2		11 (8.0–30)	0.7 (0–9.3)	79	63[d]	5
El-Mofty et al. [49]	10	Skin type[b]	0.5 J/cm^2	2	18.7 ± 5.61	24.16 ± 20.07	5.6 ± 6.88		51[d]	2
	10	Skin type[b]	0.5 J/cm^2	3	35.33 ± 2.00	21.16 ± 15.40	5.88 ± 5.24		49[d]	
Sivanesan et al. [51]	30	Skin type[b]	0.5–3.0 J/cm^2	3		15.3 (7.7–28.3)	2.66		63	5

Table 5 continued

Trial	No. of participants	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[c] [mean ± SD, or mean (range)]	Result PASI[c] [mean ± SD, or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[e] [16]
Dayal et al. [23]	30	Skin type[b]	20 %	2	12.7	21.6 ± 4.42	1.39 ± 0.39		100	3
Chauhan et al. [22]	21	Skin type[b]	1–1.5 J/cm^2 every 2nd Rx	3	30	16.9 ± 4.7			82	2

MPD minimal phototoxic dose, *PUVA* psoralen and UVA, *Rx* treatment, *result PASI* PASI at the end of the study

[a] Within patient comparison trial

[b] Skin type: starting dose is based on the Fitzpatrick skin type

[c] PASI: Psoriasis Area and Severity Index

[d] Estimated PASI-75

[e] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

Table 6 Trials with PUVA/combination

Trial	No. of participants	Intervention	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[b] [mean (range)]	Result PASI[b] [mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[c] [16]
Torras et al. [52]	60	PUVA + calcipotriol	Skin type[a]	0.5 J/cm^2 every 2 treatments	3	22.1 ± 6.9	17.36 (15.93–18.8)	2.65 (1.22–4.08)		88	3
Lauharanta et al. [50]	20	PUVA preceded by etretinate	1–1.5 J/cm^2		3	15.6			25	85	2
	20	PUVA + etetinate	1–1.5 J/cm^2		3	15.9			65	90	2
Saurat et al. [55]	23	PUVA + etretinate	Skin type[a]	0.5 J/cm^2	3	16.9			80		3
	20	PUVA + acitretin	Skin type[a]	0.5 J/cm^2	3	13.7			94		3
Ozdemir et al. [30]	30	PUVA + acitretin	70 % MPD	20 % weekly	3	20	16.8 (11.2–29.3)	4.2 (1.7–11.8)		63	

MPD minimal phototoxic dose, *PUVA* psoralen and UVA, *result PASI* PASI at the end of the study

[a] Skin type: starting dose is based on the Fitzpatrick skin type

[b] PASI: Psoriasis Area and Severity Index

[c] Quality (Jadad) score: is 0-5 score, based on the randomization, double blinding, and reporting of withdrawal

Table 7 Trials with bath PUVA

Trial	No. of participants	Intervention	Starting dose	Dose increments	Dose frequency (per week)	No. of treatments [mean ± SD]	Baseline PASI[c] [mean ± SD or mean (range)]	Result PASI[c] [mean ± SD or mean (range)]	Patients achieving clearance (%)	Patients achieving PASI-75 or above (%)	Quality score[f] [16]
Collins and Rogers [48]	22	Bath PUVA (8-MOP 3.78 mg/L)	Skin type[b]	0.1–0.5 J/cm^2 every 3rd Rx	3	16.1 ± 4.1			64	64	3
Calzavara-Pinton [41][a]	12	Bath PUVA (8-MOP 0.0003 %)	50 % MPD	20–30 %	4	13	13.47 ± 3.44	4.34 ± 3.36		42[d]	2
Dawe et al. [34][a]	28	Bath PUVA (TMP 0.33 mg/L)	40 % MPD	20 %	2	24			54		3
Snellman et al. [26][a]	18	Bath PUVA (TMP 0.33 mg/L)	0.05–0.07 J/cm^2	20–30 %	3	30	8.6 (1.8–14.4)	3.5 (0–9.6)		18	3
Vongthongsri et al. [56]	20	Bath PUVA (8-MOP 1 mg/L)	50 % MPD	15–30 % every 3rd Rx	4	22	11.7 (7.5–32.8)	3.3 (0.6–11.2)		48[d]	3
	12	Bath PUVA (8-MOP 5 mg/L)	50 % MPD	15–30 % every 3rd Rx	4	23	10.8 (6.6–20.7)	1.4 (0–3.2)		64[d]	
Lauharanta and Geiger [57]	17	Bath PUVA (TMP 0.33 mg/L) + acitretin	0.06 J/cm^2	To 0.15, 0.25 to 0.4 J/cm^2 weekly	3	17.3	22.6 ± 7.1	0.6 ± 0.6	100	100[e]	3
	17	Bath PUVA (TMP 0.33 mg/L) + etretinate	0.06 J/cm^2	To 0.15, 0.25 to 0.4 J/cm^2 weekly	3	17.5	19.4 ± 7.8	1 ± 0.5	100	100[e]	

8-MOP 8-methoxypsoralen, *MPD* minimal phototoxic dose, *PUVA* psoralen and UVA, *result PASI* PASI at the end of the study, *Rx* treatment, *TMP* trimethylpsoralen

[a] Within patient comparison trial

[b] Skin type: starting dose is based on the Fitzpatrick skin type

[c] PASI: Psoriasis Area and Severity Index

[d] Estimated PASI-75

[e] PASI-90

[f] Quality (Jadad) score: is 0–5 score, based on the randomization, double blinding, and reporting of withdrawal

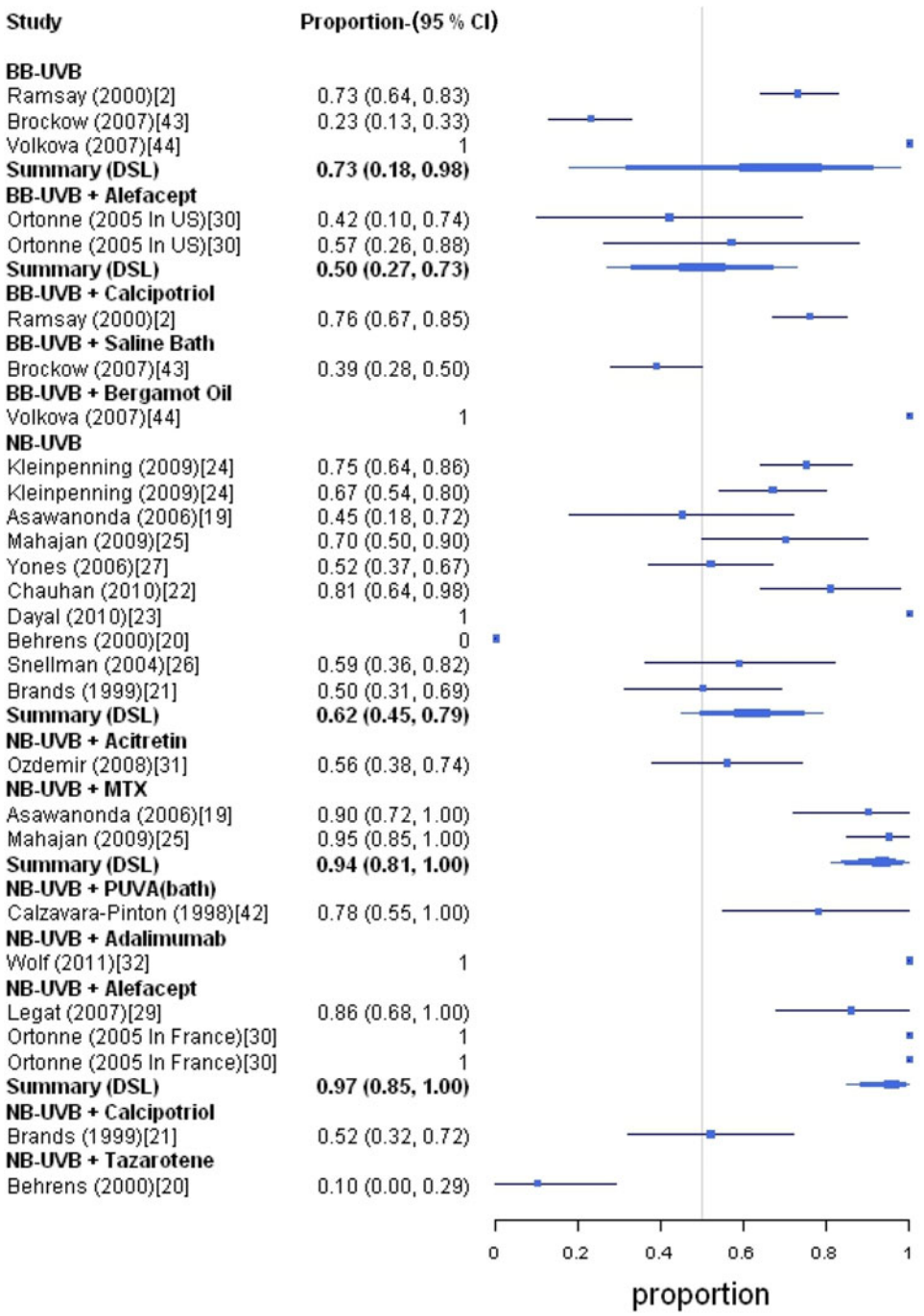

Fig. 2 Rate of PASI-75 or above for NB-UVB and BB-UVB trials. *BB-UVB* broad-band UVB, *DSL* DerSimonian-Laird method, *MTX* methotrexate, *NB-UVB* narrow-band UVB, *PASI* Psoriasis Area and Severity Index, *PASI-75* percentage of patients that achieved 75 % reduction in their baseline PASI

In contrast to the addition of alefacept to NB-UVB [28, 29], combination of alefacept and BB-UVB therapy did not show an increase in the efficacy (50 % achieving PASI-75) [29] compared with BB-UVB alone (73 % PASI-75) [2, 42, 43].

4.2.2 Mean Percentage of Patients Achieving Clearance

Prior to the use of the PASI score, clearance was often used to report the efficacy of treatment; many BB-UVB studies used this criterion. The average clearance rate of BB-UVB monotherapy from four trials with 148 patients was 59 % (95 % CI 44–72) (Fig. 3) [1, 2, 44, 45]. Combining BB-UVB with fluocinonide cream or tar oil showed a clearance rate of 54 % (BB-UVB/fluocinonide) and 63 % (BB-UVB/tar oil), respectively [44, 45]. Three trials with a total of 202 patients evaluated the addition of calcipotriol 50 μg/g cream and ointment to BB-UVB; this combination showed an average clearance rate of 56 % (95 % CI 47–64) (Table 4) [2, 46, 47]. Based on the above studies, one can

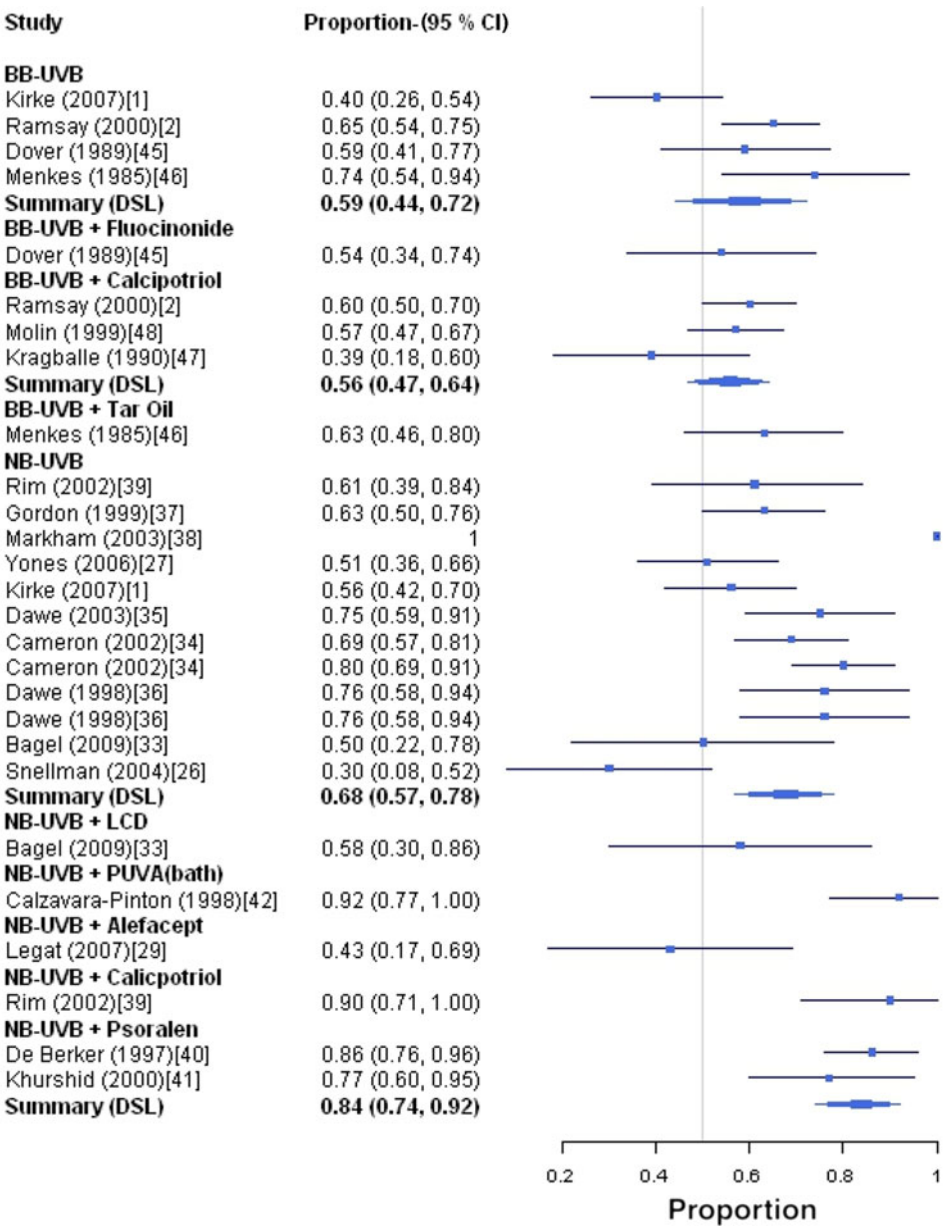

Fig. 3 Rate of clearance for NB-UVB and BB-UVB trials. *BB-UVB* broad-band UVB, *DSL* DerSimonian-Laird method, *LCD* liquor carbonis detergens (coal tar), *NB-UVB* narrow-band UVB, *PUVA* psoralen and UVA

conclude that the addition of fluocinonide cream, tar oil, and calcipotriol cream or ointment offer no advantage in regard to clearance rate as compared with BB-UVB monotherapy.

4.3 Oral Psoralen and UVA (PUVA)

4.3.1 Mean Percentage of Patients Achieving PASI-75

The average percentage of patients achieving PASI-75 for PUVA monotherapy from eight trials with 246 patients was 73 % (95 % CI 56–88) (Fig. 4) [22, 23, 27, 48–52]. In a study evaluating the combination of oral PUVA and acitretin, only 63 % of the 30 investigated patients achieved PASI-75 [30]. Combining PUVA with calcipotriol showed good efficacy in one trial, with 88 % of the 60 patients meeting PASI-75 (Table 6) [52].

4.3.2 Mean Percentage of Patients Achieving Clearance

The mean clearance rate of PUVA monotherapy from ten trials with 372 patients was 79 % (95 % CI 69–88) (Fig. 5) [27, 36, 37, 41, 40, 48, 50, 53–55]. A study [56] evaluated the combination of oral PUVA and acitretin in 20 patients; it showed a clearance rate of 94 %, which was much higher than a similar study [30] which showed PASI-75 of 63 % (Table 6).

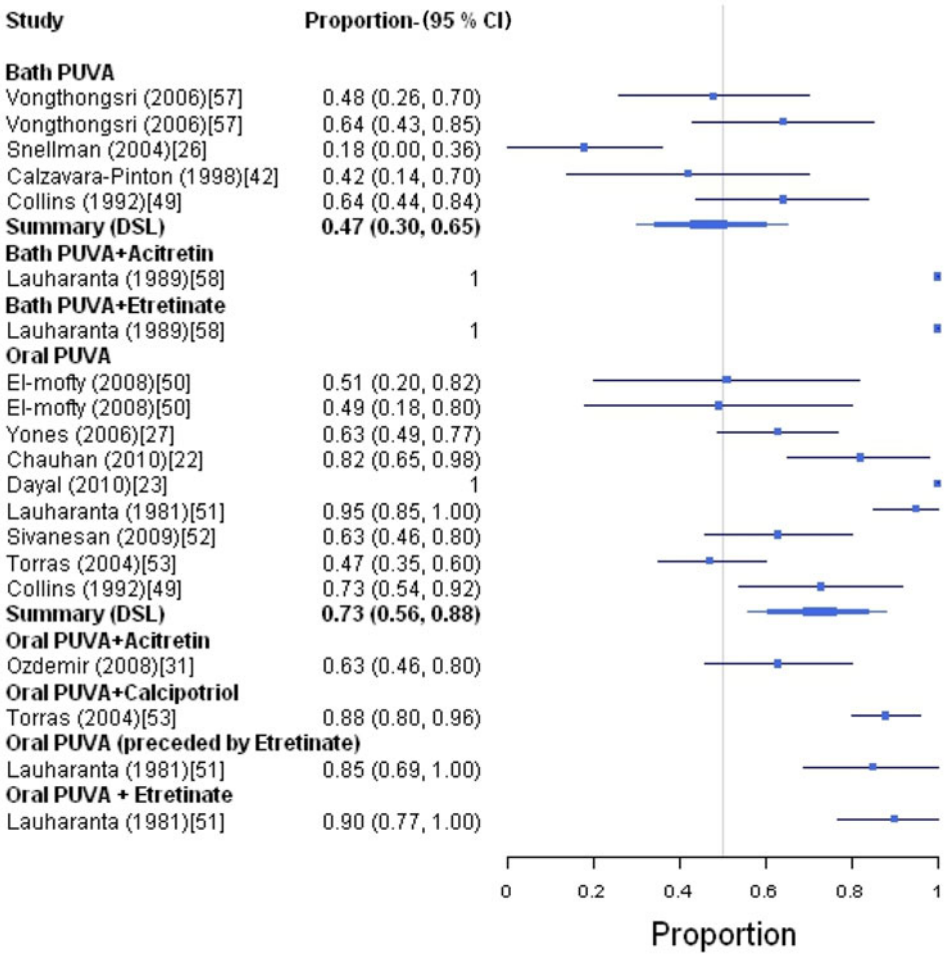

Fig. 4 Rate of PASI-75 or above for PUVA trials. *DSL* DerSimonian-Laird method, *PASI* Psoriasis Area and Severity Index, *PASI-75* percentage of patients that achieved 75 % reduction in their baseline PASI, *PUVA* psoralen and UVA

4.4 Bath PUVA

4.4.1 Mean Percentage of Patients Achieving PASI-75

The mean PASI-75 for the bath PUVA monotherapy from four trials with 84 patients was 47 % (95 % CI 30–65) (Fig. 4) [26, 41, 48, 56]. A study [56] evaluated two different concentrations (1 vs. 5 mg/L) of 8-MOP in bath PUVA; it showed an estimated PASI-75 of 56 % (95 % CI 40–71) for the two groups combined. However, the estimated PASI-75 was 64 % for the 5 mg/L group vs 48 % for the 1 mg/L group (Table 7) [56]. Another study [48] used 3.78 mg/L concentration of 8-MOP, showing that the PASI-75 and clearance rate were identical at 64 % [48], which was similar to the result with a 5 mg/L (8-MOP) group in the study by Vongthongsri et al. [56]. Two studies used trimethylpsoralen 0.33 mg/L. In Dawe et al. [34], 54 % achieved clearance, and in Snellman et al. [26], only 18 % achieved PASI-75. Both studies showed lower efficacy compared with studies using high concentration 8-MOP (3.78 and 5 mg/L) [48, 56]. A study [57] investigated the combination of bath PUVA with acitretin or etretinate; it reported 100 % of the 34 patients achieved ≥PASI-75 (Table 7) [57]. Therefore, the addition of oral retinoids to bath PUVA appeared to greatly increase the efficacy of bath PUVA.

4.4.2 Mean Percentage of Patients Achieving Clearance

The mean clearance rate of bath PUVA monotherapy from two trials with 50 patients was 58 % (95 % CI 44–72) (Fig. 5) [34, 48]. Combining bath PUVA with acitretin or etretinate in 34 patients resulted in a 100 % clearance rate in both groups (Table 7) [57].

4.5 Trials that Evaluated Different Protocols

Three studies compared different treatment protocols for NB-UVB (Table 1). Cameron et al. [33] compared frequencies of twice a week versus three times a week. They found the three-times-a-week frequency to have 80 % clearance compared with 69 % for twice weekly [33]. Similarly, Dawe et al. [35] compared frequencies of three

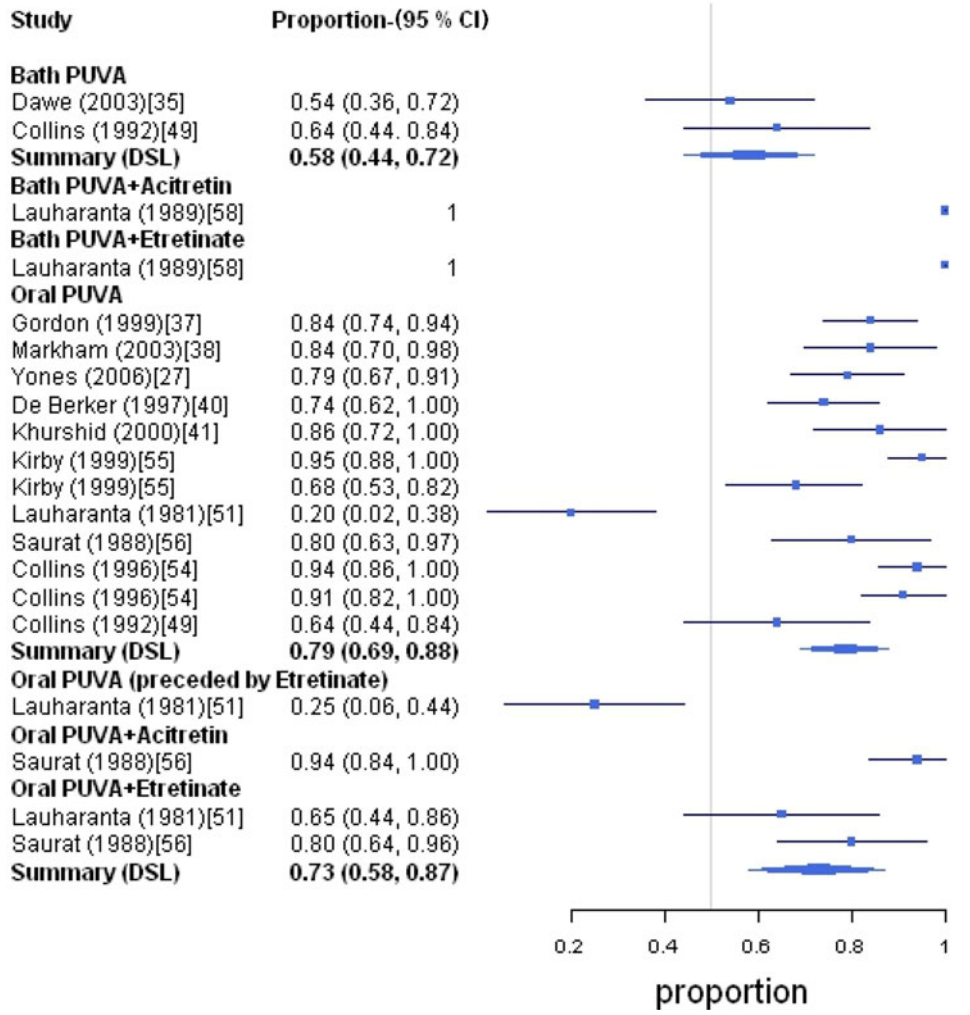

Fig. 5 Rate of clearance for PUVA trials. *DSL* DerSimonian-Laird method, *PASI* Psoriasis Area and Severity Index, *PASI-75* percentage of patients that achieved 75 % reduction in their baseline PASI, *PUVA* psoralen and UVA

times versus five times a week and found an equal clearance rate of 76 % for both groups [35]. However, fewer treatments were needed to achieve clearance in the three times weekly group versus the five times weekly group. Kleinpenning et al. [24] compared an aggressive NB-UVB protocol of a 40 % increase with a 20 % increase with each treatment. While there was a difference in the percentage of patients achieving PASI-75 (75 vs. 67 %) in favor of an aggressive protocol with a mean of four fewer treatments, this difference was not statistically significant [24]. Therefore, the above studies suggest that three times a week frequency with a 20 % increase with each treatment is a reasonable approach. However, it should be noted that these studies were performed on Caucasian patients with Fitzpatrick skin phototypes I, II, and III.

Three PUVA studies investigated different protocols (Table 5). El-Mofty et al. [49] compared two times with three times a week frequency; they found no significant difference in efficacy between the two groups; however, the three times a week group received double the number of treatments [49]. Two studies evaluated different PUVA starting dose protocols [i.e., minimal phototoxic dose (MPD)-based vs. skin type-based]. Even though both studies showed no advantage in starting based on MPD as compared with skin type, it was difficult to draw a firm conclusion because the increment protocols for MPD and skin type groups were different [53, 54].

4.6 Safety and Tolerability of UV-Based Therapy

The average percentages of asymptomatic erythema development were 57 % for NB-UVB [1, 19, 23, 25, 27, 32–38], 64 % for BB-UVB [1, 42, 43], 45 % for PUVA [23, 27, 36, 37, 40, 48, 50, 51, 53, 54], and 34 % for bath PUVA monotherapy studies (Tables 8, 9, 10, 11, 12) [34, 48]. Symptomatic erythema or blistering for the monotherapy studies were as follows: 7.8 % for NB-UVB [1, 26, 27, 33–36, 38], 2 % for BB-UVB [1, 42, 43], 17 % for PUVA [27, 36, 39, 51, 53], and 21 % for bath PUVA (Tables 8, 9, 10, 11, 12) [34, 41, 56]. The combination of oral 8-MOP with NB-UVB resulted in asymptomatic erythema or blistering in 12 % of the patients, which is higher than NB-UVB but

Table 8 Adverse effects and withdrawal due to adverse effects for NB-UVB trials

Trial	No. of patients	Asymptomatic erythema (%)	Symptomatic erythema or blistering (%)	Withdrawal due to adverse effects (%)
Kleinpenning et al. [24]	55	NR	NR	2
	54	NR	NR	2
Asawanonda and Nateetongrungsak [19]	13	15	NR	7
Rim [38]	18	11	5	5
Mahajan et al. [25]	20	25	NR	10
Gordon et al. [36]	51	73	2	0
Markham et al. [37]	24	75	NR	3
Yones et al. [27]	45	22	7	6
Chauhan et al. [22]	21	NR	NR	NR
Kirke et al. [1]	50	86	4	6
Dayal et al. [23]	30	100	NR	NR
Dawe et al. [34][a]	28	75	14	7
Cameron et al. [33]	58	69	17	3
	55	73	21	2
Dawe et al. [35][a]	21	18	0	0
		93	0	0
Behrens et al. [20][a]	10	NR	NR	NR
Bagel [32][a]	12	25	NR	0
Snellman et al. [26][a]	17	NR	29	0
Brands et al. [21]	28	NR	NR	0
DSL[b]	**NR**	**57**	**7.80**	**2**

NB-UVB narrow-band UVB, *NR* not reported

[a] Within patient comparison trial

[b] DSL = DerSimonian-Laird method, which is considering random effect from each study

lower than PUVA [39], whereas the combination of bath PUVA and NB-UVB greatly increased the asymptomatic erythema or blistering to 50 % (Table 9) [41]. The mean percentage of nausea/vomiting from PUVA studies was 33 % (Table 11) [22, 23, 36, 40, 48, 51, 53]. Details of the adverse effects for both monotherapy and combination studies are described in Tables 8, 9, 10, 11, 12.

Tolerability as measured by the percentage of withdrawal due to adverse effects was 2 % for NB-UVB [1, 19, 21, 24–27, 32–38], 4.6 % for BB-UVB [1, 2], 5 % for PUVA [27, 36, 37, 48, 51–55], and 0.7 % for bath PUVA monotherapy [26, 34, 41, 48, 56]. The percentages of the withdrawal due to adverse effects for all the included studies are shown in Tables 8, 9, 10, 11, 12.

5 Discussion

In this systematic review, we assessed the efficacy, short-term safety, and tolerability of different UV-based therapeutic modalities in the treatment of moderate to severe plaque psoriasis. The results are summarized in Table 13. With regard to PASI-75 (Figs. 2, 3), we found PUVA to be the most effective modality with an average of 73 % of patients achieving PASI-75 [22, 23, 27, 48–52]. The three trials with BB-UVB also showed a high PASI-75 (73 %) but with a wide confidence interval (18–98) [2, 42, 43]. This was followed by NB-UVB (62 %) [19–27], then bath PUVA (47 %) [26, 41, 48, 56]. Based on clearance rate (Figs. 3, 5), 79 % of PUVA patients achieved clearance [27, 36, 37, 39, 40, 48, 50, 53–55] followed by NB-UVB (68 %) [1, 26, 27, 32–38], BB-UVB (59 %) [1, 2, 44, 45], then bath PUVA (58 %) [34, 48]. The clearance end point was more accurate than PASI-75. The reason is that all results according to clearance were reported in the trials, but PASI-75 was not reported in all the trials with the PASI scoring. Our estimation of PASI-75 from these trials does not reflect the real number of patients who achieved PASI-75, but only an estimation of the number of patients that might have achieved PASI-75 if the mean baseline PASI and end of the study PASI follow the normal distribution pattern. This resulted in the dilution of the real PASI-75 as evident by the estimated PASI-75 being lower than the reported clearance in the same study [27].

Table 9 Adverse effects and withdrawal due to adverse effects for NB-UVB/combination trials

Trial	No. of patients	Intervention	Asymptomatic erythema (%)	Symptomatic erythema or blistering (%)	Withdrawal due to adverse effects (%)
Bagel [32][a]	12	NB-UVB + LCD	25	NR	0
Behrens et al. [20][a]	10	NB-UVB + tazarotene	NR	NR	NR
Rim et al. [38]	10	NB-UVB + calcipotriol	20	NR	10
Brands et al. [21]	25	NB-UVB + calcipotriol	NR	NR	8
DSL[b]		**NB-UVB + calcipotriol**	**20**	**NR**	**8**
Ortonne et al. [29]	10	NBUVB + alefacept 6 wks	19	NR	10
	11	NB-UVB + alefacept 12 wks	NR	NR	NR
Legat et al. [28]	14	NB-UVB + alefacept	NR	NR	7
DSL[b]		**NB-UVB + alefacept**	**19**	**NR**	**8**
Wolf et al. [31]	4	NB-UVB + adalimumab	50	0	0
Asawanonda and Nateetongrungsak [19]	11	NB-UVB + methotrexate	18	NR	NR
Mahajan et al. [25]	20	NB-UVB + methotrexate	10	NR	5
DSL[b]		**NB-UVB + methotrexate**	**12**	**NR**	**5**
Ozdemir et al. [30]	30	NB-UVB + acitretin	37	3	3
De Berker et al. [39]	50	NB-UVB + psoralen	44	12	2
Khurshid et al. [40]	22	NB-UVB + psoralen	NR	NR	NR
Calzavara-Pinton [41][a]	12	NB-UVB + bath PUVA	NR	50	NR

LCD liquor carbonis detergens (coal tar), *NB-UVB* narrow-band UVB, *NR* not reported, *PUVA* psoralen and UVA

[a] Within patient comparison trial

[b] DSL = DerSimonian-Laird method, which is considering random effects from each study

We also assessed the efficacy of combinations of UV-based therapeutic modalities with topical, systemic, and biologic agents. However, the numbers of patients in each of the combinations are generally low compared with the number of patients treated with UV-based monotherapy. The most effective combinations with NB-UVB were adalimumab, alefacept, and methothrexate, with PASI-75 scores of 100 % (adalimumab) [31], 97 % (alefacept) [28, 29], and 94 % (methotrexate), [19, 25] respectively (Table 2). Also, the combination of NB-UVB with bath PUVA was very effective with 92 % of the patients reaching clearance [41], but this combination resulted in high symptomatic erythema or blistering adverse effects (50 %). The use of psoralen with NB-UVB resulted in 84 % clearance (Fig. 3) [39, 40], a rate close to the PUVA clearance rate (79 %). However, it should be noted that the long-term safety of combining psoralen with NB-UVB is not yet established, and there is a theoretical risk of increasing the incidence of skin cancers due to the formation of more than one type of DNA photoadducts [58]. The combination of calcipotriol ointment 50 μg/g with NB-UVB showed inconsistent results. In one study, the estimated PASI-75 was 52 % [21], whereas in another study the clearance rate was 90 % (Table 2) [38]. One possible explanation for the high rate of clearance in the second study is that the mean number of exposures to NB-UVB in this study was 43 treatments, which is more than the other study (31 treatments).

Fifty percent of patients receiving combination of alefacept with BB-UVB achieved PASI-75 [29], which is not better than BB-UVB alone (73 %) [2, 42, 43]. Combination of BB-UVB with calcipotriol showed the achievement of ≥PASI-75 in 76 % of the patients in one study [2]. However, the average clearance rate in three studies was 56 % [2, 46, 47], which is similar to the clearance rate of BB-UVB alone (59 %) (Fig. 3) [1, 2, 44, 45]. A combination of fluocinonide cream or tar oil with BB-UVB showed a clearance rate of 54 % (fluocinonide cream) [44] and 63 % (tar oil) [45], respectively (Table 4), which is close to the clearance rate of BB-UVB alone (59 %). It is possible that the combination of topical treatments with NB-UVB or BB-UVB may have an effect

Table 10 Adverse effects and withdrawal due to adverse effects for BB-UVB trials

Trial	No. of patients	Intervention	Asymptomatic erythema (%)	Symptomatic erythema or blistering (%)	Withdrawal due to adverse effects (%)
Ramsay et al. [2]	80	BB-UVB	NR	NR	5
Brockow et al. [42]	64	BB-UVB	77	4	NR
Valkova [43]	102	BB-UVB	29	0	NR
Dover et al. [44]	29	BB-UVB	NR	NR	NR
Menkes et al. [45]	19	BB-UVB	NR	NR	NR
Kirke et al. [1]	50	BB-UVB	84	6	4
DSL[b]		**BB-UVB**	**64**	**2**	**4.60**
Menkes et al. [45]	30	BB-UVB + tar oil	NR	NR	NR
Dover et al. [44]	24	BB-UVB + fluocinonide	NR	NR	NR
Valkova [43]	91	BB-UVB + bergamot oil	44	24	NR
Brockow et al. [42]	79	BB-UVB + saline bath	85	4	2
Kragballe [46][a]	20	BB-UVB + calcipotriol	NR	NR	0
Ramsay et al. [2]	84	BB-UVB + calcipotriol	NR	NR	1
Molin et al. [47] series A[a]	98	BB-UVB + calcipotriol	17	5	4
DSL[b]		**BB-UVB + calcipotriol**	**17**	**5**	**2**
Ortonne et al. [29]	9	BB-UVB + alefacept 6 wks	79	NR	11
	10	BB-UVB + alefacept 12 wks	NR	NR	10
DSL		**BB-UVB + alefacept**	**79**	**NR**	**10.50**

BB-UVB broad-band UVB, *NR* not reported

[a] Within patient comparison trial

[b] DSL = DerSimonian-Laird method, which is considering random effect from each study

on decreasing the number of treatments and hence, the total cumulative dose of UVB [58]. However, our analysis was not designed to assess this endpoint.

The combination of PUVA with acitretin showed inconsistent results with 63 % achieving PASI-75 in one study [30], and 94 % achieved clearance in another study (Table 6) [55]. However, a trial combining bath PUVA with retinoid (acitretin or etretinate) resulted in all patients (100 %) achieving ≥PASI-75 and clearance (Table 7) [57]. This finding was not replicated in other studies. The addition of retinoid to PUVA also may have a protective effect in decreasing the long-term risk of photocarcinogenesis associated with PUVA. The combination of topical calcipotriol and PUVA was shown in one trial to increase the efficacy of PUVA [52].

In this review, we found oral PUVA to be more effective than NB-UVB in the treatment of widespread plaque psoriasis. We also found NB-UVB to be more effective than BB-UVB based on clearance as an end point. This was consistent with the conclusion of a quantitative review by Dawe in 2003 evaluating the efficacy of NB-UVB and BB-UVB in the treatment of psoriasis, which included 11 studies that suggested NB-UVB to be more effective than BB-UVB [59]. Ashcroft et al. [60] conducted a systematic review investigating the combination of topical calcipotriol with UVB in the treatment of plaque psoriasis [60]. They found no advantage of the combination versus UVB monotherapy. However, they did not separate NB-UVB from BB-UVB studies. In our review, no consistent advantage was noted in combining topical calcipotriol either with BB-UVB, or with NB-UVB.

Similar to calcipotriol, combining other topical treatments such as tazarotene, fluocinonide, and tar oil with UVB showed no obvious advantage over UVB alone.

On the other hand, the combination of NB-UVB with methotrexate, or with biologics such as alefacept or adalimumab, was highly effective. However, because of potential long-term adverse effects (UVB/methotrexate

Table 11 Adverse effects and withdrawal due to adverse effects for PUVA trials

Trial	No. of patients	Intervention	Asymptomatic erythema (%)	Nausea/ vomiting (%)	Symptomatic erythema or blistering (%)	Withdrawal due to adverse effects (%)
El-Mofty et al. [49]	10	PUVA	NR	NR	NR	NR
	10	PUVA	NR	NR	NR	NR
Gordon et al. [36]	51	PUVA	35	4	12	4
Markham et al. [37]	25	PUVA	80	NR	NR	8
Yones et al. [27]	43	PUVA	49	NR	14	4
Chauhan et al. [22]	21	PUVA	NR	27	NR	NR
Dayal et al. [23]	30	PUVA	70	75	NR	NR
De Berker et al. [39]	50	PUVA	NR	NR	20	NR
Khurshid et al. [40]	22	PUVA	4.5	18	NR	NR
Kirby et al. [54]	40	PUVA	52.5	NR	NR	2.5
	40	PUVA	45	NR	NR	25
Lauharanta et al. [50]	20	PUVA	60	NR	NR	0
Saurat et al. [55]	22	PUVA	NR	NR	NR	6
Collins et al. [53][a]	37	PUVA	54	24	9	3
		PUVA	12	24	NR	NR
Sivanesan et al. [51]	30	PUVA	60	63.3	36.7	20
Torras et al. [52]	60	PUVA	NR	NR	NR	3
Collins and Rogers [48]	22	PUVA	31.8	40.9	NR	9
DSL[b]		**PUVA**	**45**	**33**	**17**	**5**
Torras et al. [52]	60	PUVA + calcipotriol	3.3	NR	NR	3
Lauharanta et al. [50]	20	PUVA (preceded by etretinate)	70	NR	NR	0
	20	PUVA + etretinate	40	NR	NR	0
Saurat et al. [55]	20	PUVA + acitretin	NR	NR	NR	6
	23	PUVA + etretinate	NR	NR	NR	6
Ozdemir et al. [30]	30	PUVA + acitretin	28	76	NR	6

NR not reported, *PUVA* psoralen and UVA

[a] Within patient comparison trial

[b] DSL = DerSimonian-Laird method, which is considering random effect from each study

combination) and cost (biologics), these combinations should be reserved for patients not responding to phototherapy alone.

The combination of topical calcipotriol with PUVA, and oral retinoid (acitretin and etretinate) with bath PUVA, greatly increased the efficacy over monotherapy, based on two studies with a limited number of patients.

Although PUVA was shown to be more effective than NB-UVB, in clinical practice, NB-UVB is currently the first-line UV-based therapy for psoriasis. This is because NB-UVB is not associated with systemic adverse effects such nausea and vomiting, it does not require eye protection on the days of treatment, and thus far, has not been shown to have carcinogenic potential. However, PUVA

Table 12 Adverse effects and withdrawal due to adverse effects for bath PUVA trials

Trial	No. of patients	Intervention	Asymptomatic erythema (%)	Symptomatic erythema or blistering (%)	Withdrawal due to adverse effects (%)
Snellman et al. [26][a]	18	Bath PUVA	NR	NR	0
Calzavara-Pinton [41][a]	12	Bath PUVA	NR	42	0
Vongthongsri et al. [56][a]	20	Bath PUVA	NR	20	0
	21	Bath PUVA	NR	19	NR
Dawe et al. [34][a]	28	Bath PUVA	57	14	3
Collins and Rogers [48]	22	Bath PUVA	13.6	NR	4.5
DSL[b]		**Bath PUVA**	**34**	**21**	**0.7**
Lauharanta and Geiger [57]	17	Bath PUVA + acitretin	NR	NR	0
	17	Bath PUVA + etretinate	NR	NR	0

NR not reported, *PUVA* psoralen and UVA

[a] Within patient comparison trial

[b] DSL = DerSimonian-Laird method, which is considering random effect from each study

Table 13 Summaries of the mean efficacy, adverse effect, and withdrawal results from the monotherapy trials evaluating NB-UVB, BB-UVB, PUVA, and bath PUVA. Values shown are percentage of patients (95 % CI)

Treatment	Patients achieving PASI-75 or above	Patients achieving clearance	Asymptomatic erythema	Symptomatic erythema or blistering	Withdrawal due to adverse effects
NB-UVB	62 (45–79)	68 (57–78)	57 (39–74)	7.8 (3.1–14)	2 (0.8–3.8)
BB-UVB	73 (18–98)	59 (44–72)	64 (26–94)	2 (0.6–8)	4.6 (1.4–9)
PUVA	73 (56–88)	79 (69–88)	45 (32–58)	17 (10–26)	5 (3–8)
Bath PUVA	47 (30–65)	58 (44–72)	34 (2–78)	21 (11–31)	0.7 (0–4)

BB-UVB broad-band UVB, *NB-UVB* narrow-band UVB, *PASI* Psoriasis Area and Severity Index, *PUVA* psoralen and UVA

clearly is an excellent option in patients who are not responsive to NB-UVB.

Based on the results of studies that evaluate different protocols for NB-UVB [24, 33, 35], we found a frequency of three times per week with 20 % increments is the most reasonable protocol. However, these studies were performed on Caucasian patients with mainly skin phototypes I, II, and III. It should be noted that a protocol that is effective for light-skinned patients is not necessary effective for dark-skinned patients. This was confirmed by Yones et al. [27], who showed a large difference in the clearance rate between light-skinned patients (74–75 %) versus dark-skinned patients (24 %) using the same protocol [27]. Future studies are needed to evaluate the optimal treatment protocol in dark-skinned patients.

Based on bath PUVA studies, 8-MOP might be more effective than trimethylpsoralen, and the highest efficacy was seen with 3.78 or 5 mg/L concentrations of 8-MOP [48, 56].

The most commonly reported adverse effects were erythema, blistering, and in PUVA studies only, nausea/vomiting. Erythema is usually dose dependent and can be controlled by the phototherapist or the physician. Symptomatic erythema or blistering was higher in bath PUVA and PUVA trials than in BB and NB-UVB studies. The combination of bath PUVA with NB-UVB greatly increases the risk of symptomatic erythema or blistering.

Despite high percentages of asymptomatic erythema, symptomatic erythema, or blistering, and nausea/vomiting (PUVA only) in the included trials, the percentage of withdrawals due to adverse effects was in general low, which suggests the mild nature of these reactions. The highest withdrawal rate was 5 % in PUVA studies [27, 36, 37, 48, 51–55], followed by BB-UVB (4.6 %) [1, 2], NB-UVB (2 %) [1, 19, 21, 24–27, 32–38], and then bath PUVA (0.7 %) (Table 13) [26, 34, 41, 48, 56].

There are limitations to this review. Many trials with PASI scores failed to report the PASI-75; therefore, we had to calculate the estimated PASI-75 assuming normal distribution of PASI changes. This results in dilution of the real PASI-75 percentage, hence underreporting of the percentage of patients achieving PASI-75. Another

limitation is the fact that there is no consistent definition of clearance used in the various studies. In order to minimize the lack of clarity on the definition of clearance, we included only studies in which the authors stated that patients had ≥90 % improvement, had complete clearance, or had complete clearance with minimal residual activity. Another limitation is that the conclusions obtained on the efficacy of combination treatments were usually the result of just a few trials, and sometimes only a single trial. As a result, the data on monotherapy are much more robust than the data on combination therapy. This review does not intend to directly compare the efficacy and safety among different therapies, and the DerSimonian and Laird pooled proportion of efficacy/safety was reported for each therapy separately [61]. All trials were treated independently to estimate the pooled effect size, although a few of them were paired (dependent) within a trial. Those indirect comparisons among therapies only report the difference without statistical assessment, and they could be considered as a direction for our future research, such as using a complex mixed model to assess the efficacy/safety among all therapies directly by controlling other confounders.

We would suggest that for future studies on UV-based therapy for chronic plaque psoriasis, the PASI scoring system needs to be used, and PASI-75 scores need to be reported. The use of clearance, even though it is the ultimate goal clinically, should be avoided. This is because there is no consistent definition of clearance; in fact, it is rarely used in other studies that evaluate the efficacy of non-UV treatments in psoriasis, which creates difficulty in comparing the efficacy of UV treatments with other treatments of psoriasis. The use of a clearly described protocol with regard to starting dose, increments, maximum dose, and the number of treatments needed to achieve the endpoints is essential in UV-based therapy studies. We would also suggest the separation of guttate psoriasis from chronic plaque psoriasis, because the self-limiting property of guttate psoriasis might overestimate the efficacy value. A measure of compliance also needs to be incorporated in UV-based therapy studies since this can greatly affect the efficacy; it should be noted that compliance is rarely reported in UV-based therapy studies.

6 Conclusion

We performed a systematic review and meta-analysis on UV-based therapy in the treatment of adults with moderate to severe plaque psoriasis. Our results, based on clearance outcome, suggest PUVA to be more effective than NB-UVB, followed by BB-UVB, and bath PUVA. Based on PASI-75, the results were similar except for BB-UVB, which showed a high mean PASI-75 (73 %) with a wide CI (18–98). This is due to the heterogeneity of the three available studies that investigated BB-UVB using the PASI score. Few trials with limited numbers of patients evaluated the combination of phototherapy with topical and systemic, including biologic, treatments. The combination of methotrexate or biologics with NB-UVB, topical calcipotriol with PUVA, and oral retinoid with bath PUVA were shown to be highly effective. Due to the limited head-to-head studies comparing biologics with phototherapy, further studies would be very helpful to all. It will help physicians, patients, and policy makers in making decisions regarding different available treatments for moderate to severe psoriasis.

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