Original paper

Efficacy of apremilast for psoriasis: a meta-analysis of randomized controlled studies

Yashu Liu[1], Yuting Li[1], Hanghang Du[2]

[1]Department of Dermatology, Banan Hospital of Chongqing Medical University, Chongqing, China
[2]Xi'an Huamei Aesthetic and Plastic Hospital, Shanxi, China

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Abstract

Introduction: The efficacy of apremilast for psoriasis remains controversial.
Aim: We have conducted a systematic review and meta-analysis to explore the influence of apremilast on treatment efficacy for psoriasis.
Material and methods: We have searched PubMed, Embase, Web of science, EBSCO, and Cochrane library databases for randomized controlled trials (RCTs) published until February 2022 and assessing the efficacy and safety of apremilast for psoriasis. This meta-analysis was performed using the random-effects model.
Results: Seven RCTs were included in the meta-analysis. Overall, compared with placebo for psoriasis, apremilast was associated with improved PASI-75 (LOCF) (OR = 6.59; 95% CI: 4.55 to 9.53; $p < 0.00001$), PASI-75 (NRI) (OR = 6.99; 95% CI: 4.43 to 11.04; $p < 0.00001$), sPGA response (LOCF) (OR = 5.58; 95% CI: 3.82 to 8.16; $p < 0.00001$), sPGA response (NRI) (OR = 6.06; 95% CI: 4.07 to 9.02; $p < 0.00001$), PASI-50 (LOCF) (OR = 4.37; 95% CI: 2.72 to 7.01; $p < 0.00001$), PASI-90 (LOCF) (OR = 7.81; 95% CI: 2.89 to 21.08; $p < 0.0001$), adverse events (OR = 1.58; 95% CI: 1.19 to 2.10; $p = 0.002$), but demonstrated no increase in serious adverse events (OR = 1.01; 95% CI: 0.43 to 2.33; $p = 0.99$).
Conclusions: Apremilast is effective and safe to treat psoriasis.

Key words: apremilast, psoriasis, efficacy, safety, randomized controlled trials.

Introduction

Psoriasis has become one common immune-mediated inflammatory disease, and its treatment is still challenging [1–5]. These patients often desire complete skin clearance and improved long-term efficacy [6–8]. In patients with psoriasis, the scalp is the most commonly affected area, and approximately 80% of psoriasis patients suffer from scalp involvement [9]. These patients have significantly reduced mental health, quality of life and social functioning [10, 11].

Topical therapies are regarded as the first-line therapeutic option for treatment of scalp psoriasis, but may provide inadequate relief for patients with moderate to severe scalp psoriasis [10, 12, 13]. These patients need systemic or biologic agents with frequent monitoring for adverse events [14, 15]. As an oral phosphodiesterase 4 inhibitor, apremilast has shown some efficacy in patients with psoriasis, including in subsets of patients with scalp involvement [16–19].

Recently, several studies have compared the efficacy of apremilast for psoriasis, but the common use of apremilast for psoriasis has not been well established [16, 17, 20, 21]. The usage of this medicine is as follows: Day 1: 10 mg in the morning, Day 2: morning 10 mg and evening 10 mg, Day 3: morning 10 mg and evening 20 mg, Day 4: morning 20 mg and evening 20 mg, Day 5: morning 20 mg and evening 30 mg, Day 6 and thereafter: 30 mg twice daily [21].

Aim

This meta-analysis of RCTs aims to assess the efficacy of apremilast for psoriasis.

Material and methods

This systematic review and meta-analysis were performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis state-

Address for correspondence: Hanghang Du, Xi'an Huamei Aesthetic and Plastic Hospital, Shanxi, China, phone: 067-63901832, fax: 067-63901832, e-mail: 15923022340@163.com
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ment and Cochrane Handbook for Systematic Reviews of Interventions [22, 23]. No ethical approval and patient consent were required because all analyses are based on previous published studies.

Literature search and selection criteria

We have systematically searched several databases including PubMed, Embase, Web of science, EBSCO, and the Cochrane library for RCTs published from inception to February 2022 with the following keywords: "apremilast" AND "psoriasis". The reference lists of retrieved studies and relevant reviews were also hand-searched and the above process was performed repeatedly in order to include additional eligible studies.

The inclusion criteria were presented as follows: (1) study design is RCT, (2) patients are diagnosed as psoriasis, and (3) intervention treatments are apremilast versus placebo.

Data extraction and outcome measures

Some baseline information was extracted from the original studies, and they included the first author, number of patients, age, body mass index (BMI), duration of psoriasis and detailed methods in two groups. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcomes were PASI-75 (LOCF) and PASI-75 (NRI). Secondary outcomes included sPGA response (LOCF), sPGA response (NRI), PASI-50 (LOCF), PASI-90 (LOCF), adverse events and serious adverse events.

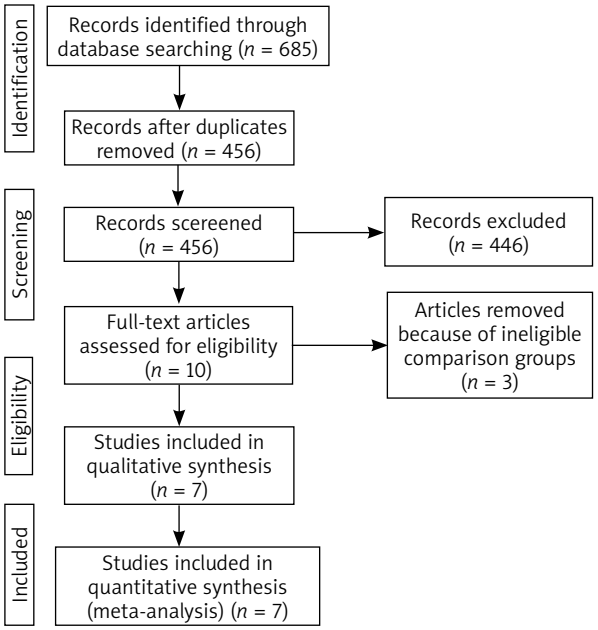

Figure 1. Flow diagram of the study searching and selection process

Quality assessment in individual studies

The methodological quality of each RCT was assessed by the Jadad Scale which consists of seven evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points) [24]. One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3 [25].

Statistical analysis

We assessed the odd ratio (OR) with 95% confidence interval (CI) for all dichotomous outcomes. Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity [26]. The random-effects model was used for all meta-analyses. We searched for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (< 10) of included studies, publication bias was not assessed. Results were considered as statistically significant for $p < 0.05$. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. Six hundred eighty-five potentially relevant articles were identified initially. Finally, seven RCTs were included in the meta-analysis [16–21, 27].

The baseline characteristics of seven included RCTs were shown in Table 1. These studies were published between 2013 and 2020, and the total sample size was 2173. Among the included RCTs, apremilast was administered at a dose of 20 mg or 30 mg twice daily for 16 weeks.

Among seven included RCTs, four studies reported PASI-75 (LOCF) [16, 17, 21, 27], three studies reported PASI-75 (NRI) [16, 17, 27], four studies reported sPGA response (LOCF) and sPGA response (NRI) [16, 17, 20, 27], four studies reported PASI-50 (LOCF) [16, 17, 21, 27], three studies reported PASI-90 (LOCF) [16, 17, 27], five studies reported adverse events [16, 17, 19, 20, 27] and six studies reported serious adverse events [16, 17, 19–21, 27]. Jadad scores of the seven included studies varied from

Table 1. Characteristics of included studies

Author	Apremilast group						Control group						Jada scores
	Number	Age	Female (*n*)	BMI [kg/m^2]	Duration of psoriasis [years]	Methods	Number	Age	Female (*n*)	BMI [kg/m^2]	Duration of psoriasis [years]	Methods	
Van Voorhees 2020	201	47.0 ±15.0	76	30.7 ±7.1	15.7 ±12.4	Apremilast 30 mg twice daily for 16 weeks	102	46.7 ±15.2	40	31.7 ±7.2	14.8 ±11.3	Placebo	5
Bissonnette 2018	50	56.6 ±8.6	30	31.1 ±5.5	–	Apremilast 30 mg twice daily for 16 weeks	50	53.6 ±13.5	49	31.0 ±6.6	–	Placebo	5
Reich 2017	84	46.0 ±13.6	34	29.2 ±5.8	19.7 ±12.7	Apremilast 30 mg twice daily for 16 weeks	83	43.4 ±14.9	25	29.5 ±6.6	16.6 ±12.1	Placebo	4
Paul 2015	274	45.3 ±13.1	98	30.9 ±6.7	17.9 ±11 .4	Apremilast 30 mg twice daily for 16 weeks	137	45.7 ±13.4	37	30.7 ±7.1	18.7 ±12.1	Placebo	5
Papp 2015	562	45.8 ±13.1	183	31.2 ±6.7	19.8 ±13.0	Apremilast 30 mg twice daily for 16 weeks	282	46.5 ±12.7	88	31.3 ±7.4	18.7 ±12.4	Placebo	4
Strand 2013	88	44.1 ±14.7	38	31.1 ±7.8	19.2 ±12.0	Apremilast 30 mg twice daily for 16 weeks	88	44.1 ±13.7	35	30.8 ±6.7	19.6 ± 11.6	Placebo	4
Papp 2013	85	48.4 ±12.3	36	–	–	Apremilast 20 mg twice daily for 16 weeks	87	43.7 ±12.4	34	–	–	Placebo	4

4 to 5, and all seven studies have high quality based on the quality assessment.

Primary outcomes: PASI-75 (LOCF) and PASI-75 (NRI)

The random-effects model was used for the analysis of primary outcomes. The results found that compared to placebo for psoriasis, apremilast was associated with improved PASI-75 (LOCF) (OR = 6.59; 95% CI: 4.55 to 9.53; $p < 0.00001$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $p = 0.41$, Figure 2) and PASI-75 (NRI) (OR = 6.99; 95% CI: 4.43 to 11.04; $p < 0.00001$) with low heterogeneity among the studies ($I^2 = 21\%$, heterogeneity $p = 0.28$, Figure 3).

Sensitivity analysis

There was no significant heterogeneity for primary outcomes, and thus we did not perform sensitivity analysis by omitting one study in each turn.

Secondary outcomes

In comparison with placebo for psoriasis, apremilast resulted in the obvious increase in sPGA response (LOCF) (OR = 5.58; 95% CI: 3.82 to 8.16; $p < 0.00001$; Figure 4), sPGA response (NRI) (OR = 6.06; 95% CI: 4.07 to 9.02; $p < 0.00001$; Figure 5), PASI-50 (LOCF) (OR = 4.37; 95% CI: 2.72 to 7.01; $p < 0.00001$; Figure 6), PASI-90 (LOCF) (OR = 7.81; 95% CI: 2.89 to 21.08; $p < 0.0001$; Figure 7), adverse events (OR = 1.58; 95% CI: 1.19 to 2.10; $p = 0.002$; Figure 8), but showed no increase in serious adverse events (OR = 1.01; 95% CI: 0.43 to 2.33; $p = 0.99$; Figure 9).

Discussion

Psoriasis often causes intense pruritus. For instance, scalp psoriasis can be a very distressing manifestation of psoriasis [10, 28]. Many systemic drugs such as etanercept and secukinumab have been developed to treat moderate to severe plaque psoriasis of the scalp in phase 3 studies of patients [29, 30]. Especially, apremilast treatment

Study or subgroup	Apremilast group Events	Total	Control group Events	Total	Weight (%)	Odds ratio, IV, random, 95% CI
Bissonnette 2018	11	50	4	50	9.2	3.24 [0.96, 11.00]
Papp 2015	186	562	15	282	45.4	8.81 [5.09, 15.25]
Paul 2015	79	274	8	137	23.7	6.53 [3.05, 13.98]
Reich 2017	33	83	10	84	21.7	4.88 [2.21, 10.80]
Total (95% CI)		**969**		**553**	**100.0**	**6.59 [4.55, 9.53]**
Total events	309		37			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.91$, $df = 3$ ($p = 0.41$); $I^2 = 0\%$

Test for overall effect: $Z = 9.99$ ($p < 0.00001$)

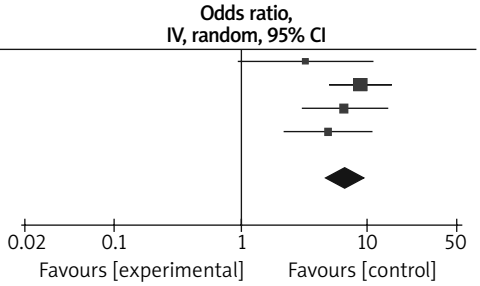

Figure 2. Forest plot for the meta-analysis of PASI-75 (LOCF)

Study or subgroup	Apremilast group Events	Total	Control group Events	Total	Weight (%)	Odds ratio, IV, random, 95% CI
Papp 2015	183	562	14	282	46.1	9.24 [5.25, 16.27]
Paul 2015	77	274	7	137	26.7	7.26 [3.25, 16.23]
Reich 2017	30	83	10	84	27.1	4.19 [1.89, 9.30]
Total (95% CI)		**919**		**503**	**100.0**	**6.99 [4.43, 11.04]**
Total events	290		31			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 2.52$, $df = 2$ ($p = 0.28$); $I^2 = 21\%$

Test for overall effect: $Z = 8.34$ ($p < 0.00001$)

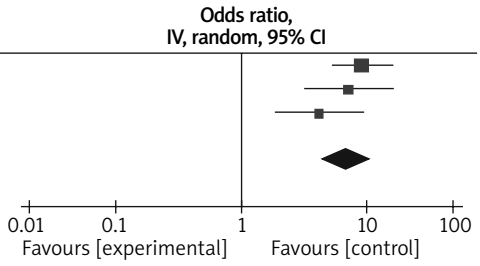

Figure 3. Forest plot for the meta-analysis of PASI-75 (NRI)

Study or subgroup	Apremilast group Events	Total	Control group Events	Total	Weight (%)	Odds ratio, IV, random, 95% CI
Papp 2015	122	562	11	282	35.7	6.83 [3.62, 12.89]
Paul 2015	56	274	6	137	19.1	5.61 [2.35, 13.38]
Reich 2017	18	83	3	84	9.0	7.48 [2.11, 26.49]
Van Voorhees 2020	81	201	14	102	36.2	4.24 [2.26, 7.97]
Total (95% CI)		**1120**		**605**	**100.0**	**5.58 [3.82, 8.16]**
Total events	277		34			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.32$, $df = 3$ ($p = 0.72$); $I^2 = 0\%$

Test for overall effect: $Z = 8.88$ ($p < 0.00001$)

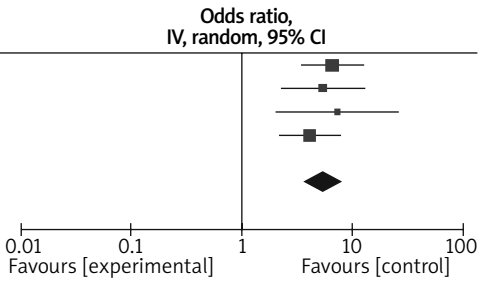

Figure 4. Forest plot for the meta-analysis of sPGA response (LOCF)

Study or subgroup	Apremilast group Events	Total	Control group Events	Total	Weight (%)	Odds ratio, IV, random, 95% CI
Papp 2015	118	562	11	282	39.0	6.55 [3.47, 12.37]
Paul 2015	54	274	5	137	17.8	6.48 [2.53, 16.61]
Reich 2017	16	83	3	84	9.7	6.45 [1.80, 23.07]
Van Voorhees 2020	78	201	11	102	33.5	5.25 [2.64, 10.43]
Total (95% CI)		**1120**		**605**	**100.0**	**6.06 [4.07, 9.02]**
Total events	266		30			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.25$, $df = 3$ ($p = 0.97$); $I^2 = 0\%$

Test for overall effect: Z = 8.89 ($p = 0.00001$)

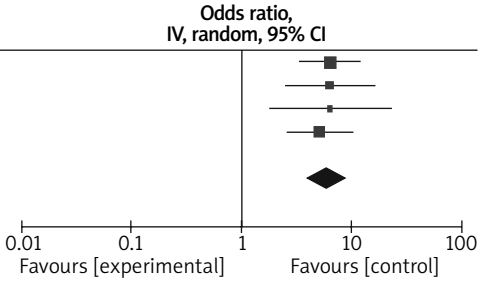

Figure 5. Forest plot for the meta-analysis of sPGA response (NRI)

was associated with significantly greater improvements in scalp psoriasis, scalp and whole body itch, and quality of life compared with placebo [17, 27].

Our meta-analysis confirmed that apremilast was able to produce significantly better treatment efficacy than control intervention for psoriasis, which was supported by the improvement in PASI-75 (LOCF), PASI-75 (NRI), sPGA response (LOCF), sPGA response (NRI), PASI-50 (LOCF) and PASI-90 (LOCF). However, we found the increase in adverse events after apremilast treatment in psoriasis patients. These adverse events mainly included diarrhoea, nausea, headache, vomiting and agitation.

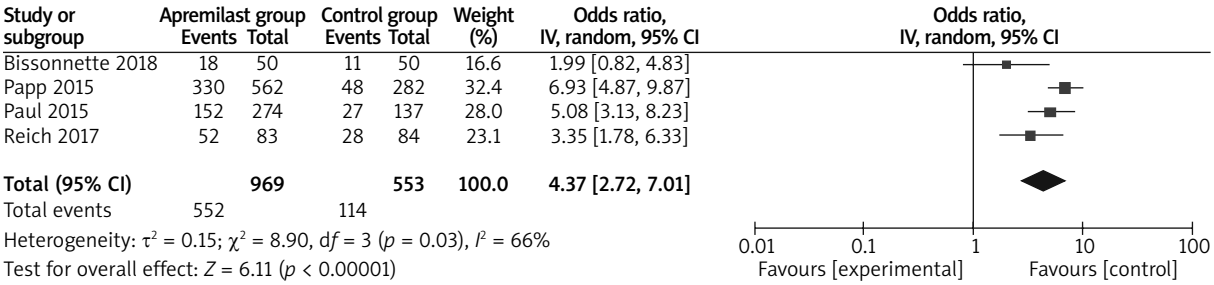

Figure 6. Forest plot for the meta-analysis of PASI-50 (LOCF)

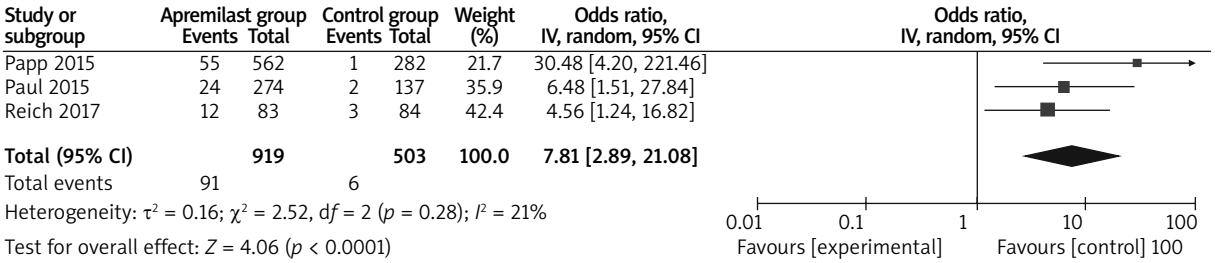

Figure 7. Forest plot for the meta-analysis of PASI-90 (LOCF)

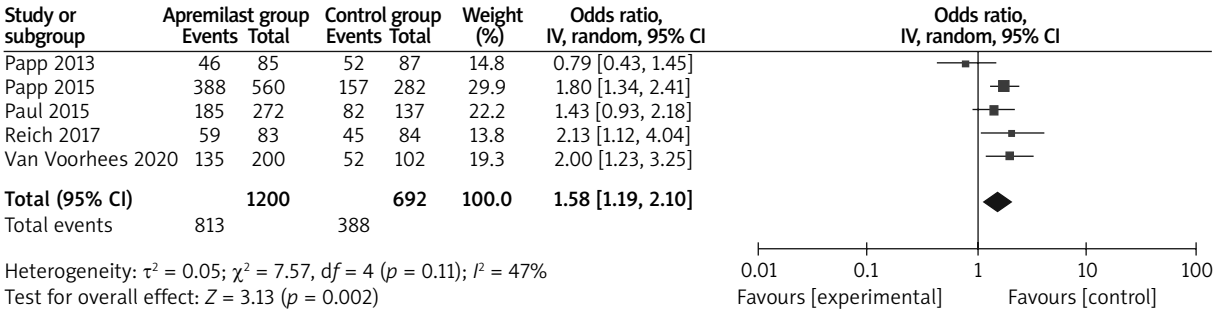

Figure 8. Forest plot for the meta-analysis of adverse events

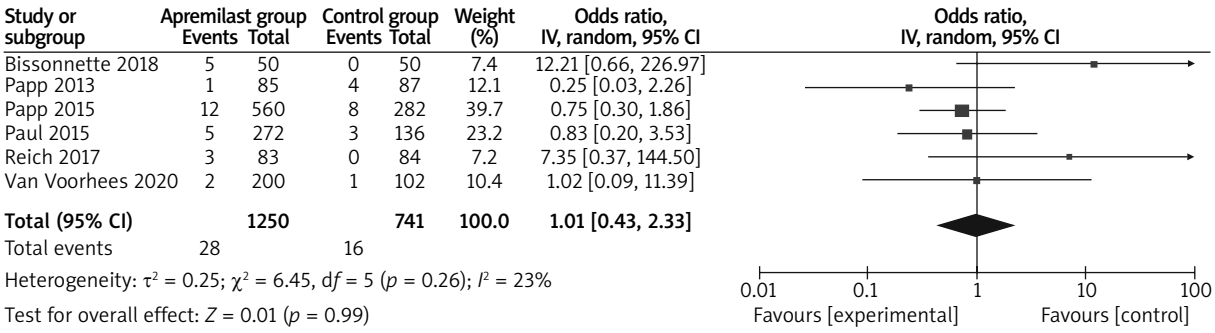

Figure 9. Forest plot for the meta-analysis of serious adverse events

They were generally acceptable and tolerant [16, 17, 21, 27]. Therefore, this meta-analysis revealed no increase in serious adverse events after apremilast treatment.

Regarding the sensitivity analysis, although no significant heterogeneity remained for the primary outcomes, several factors may produce some bias. Firstly, the apremilast was administered at a dose of 20 mg or 30 mg twice daily, and different doses of apremilast may produce some heterogeneity. Secondly, various kinds of psoriasis were included in this meta-analysis, including plaque psoriasis

of the scalp and palmoplantar psoriasis. Thirdly, different duration of psoriasis history may produce some impact on the efficacy assessment of apremilast.

Several limitations exist here. Firstly, our analysis was based on only seven RCTs, and more RCTs with a larger sample size should be conducted to explore this issue. Next, different doses of apremilast and various kinds of psoriasis were included, which may generate some bias. Finally, ideal methods for apremilast remain elusive.

Conclusions

Apremilast is effective and safe for the treatment of psoriasis.

Acknowledgments

Co-first authors: Yashu Liu, Yuting Li.

Conflict of interest

The authors declare no conflict of interest.

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