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Original Article

Efficacy and safety of secukinumab in the treatment of moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials

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Abstract: Psoriasis is a chronic inflammatory skin disease with high rate of recurrence. New anti-interleukin-17 (IL-17) and anti-IL17RA biologics are in Phase 3 clinical trials and may prove to be more effective than existing biologic drugs. Now we perform a meta-analysis on efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis. In this meta-analysis, data analysis was performed with the Cochrane Collaboration's RevMan 5.0 software. Eight randomized controlled trials (RCTs) with a total of 3,213 psoriasis cases were included in the meta-analysis. Co-primary endpoints (week 12) were ≥ 75%/90% improvement in psoriasis area and a score of 0 (clear) or 1 (almost clear) on a 5-point Investigator's Global Assessment scale (IGA mod 2011 0/1) versus placebo [1]. The overall efficacy in the meta-analysis was as follows: PASI 75: for secukinumab 150 mg versus placebo, fixed-effects OR = 49.25, 95% CI: 33.67-72.06, Z = 20.07, P < 0.00001; PASI 90: for secukinumab 150 mg versus placebo, fixed-effects OR = 44.92, 95% CI: 24.72-81.62, Z = 12.49, P < 0.00001; IGA mod 2011 0/1: for secukinumab 150 mg versus placebo, random-effects OR = 22.25, 95% CI: 7.63-64.84, Z = 5.68, P < 0.00001; Compared with placebo, there were no significant adverse effects in the secukinumab groups, demonstrating safety in the treatment of moderate to severe plaque psoriasis. The proportion of patients who achieved 75%, 90% and IGA mod 2011 0/1 reductions respectively was significant in the secukinumab groups, demonstrating a rapid clinical improvement accompanied by a favorable short-term safety profile.

Keywords: Psoriasis, secukinumab, meta-analysis

Introduction

Psoriasis is a common, chronic disease, which for many people is associated with profound functional, psychological and social morbidity and important co-morbidities such as cardiovascular disease, diabetes mellitus, obesity, and metabolic syndrome [2]. It affects 1-3% of the population in the world. The treatment of psoriasis has become a global problem. It is generally considered a genetic disease, thought to be triggered or influenced by environmental factors [3]. With the development of immunology, many clinicians and researchers came to recognize that the pathogenesis of psoriasis is primarily caused by the autoimmune disorders. Currently the drug used in clinical treatment of psoriasis is mainly on the immune system. Although the most common therapies used for moderate to severe plaque psoriasis were acitretin, cyclosporine, and methotrexate, which have some effects [4]. They can not fully meet the needs of patients, and sometimes the disease may recur and bring great pain to the patients. And the adverse effects of conventional systemic therapies are common concerns in the clinical prescribes [5]. Considering the adverse effects and limited therapeutic effect from the systemic therapies, many clinicians began to study the curative effects and safety of biological agents. Now we set sights on the efficacy and safety of a new biological drug, secukinumab.

Currently, clinicians prescribe treatment regimen for psoriasis depending on a variety of fac-

Table 1. The general information of patients included in the meta-analysis

Study	Country		Age (yeas) (mean ± SD)	Male (n)	Caucasion (n)	Duration of Psoriasis (years), mean ± SD	Psoriatic arthritis present, n
Wolf gang. Hueber	U.S.A	150 mg	50.7 ± 8.73	11	17		
		placebo	50.9 ± 12.04	13	17		
K.A . PaPP	Canada	150 mg × 3	45.4 ± 11.64	21	20	16.2 ± 10.41	5
		placebo	45.9 ± 10.88	14	17	21.4 ± 14.8	6
P. Rich	U.S.A	150 mg × 1	42.7 ± 11.32	50	59	17.5 ± 10.05	15
		150 mg × 3	44.2 ± 12.96	104	120	16.9 ± 11.47	45
		150 mg × 4	44.5 ± 12.45	133	118	17.4 ± 11.82	39
		placebo	44.2 ± 12.59	67	56	15.4 ± 10.70	12
C. Paul	France	300 mg × 6	46.6 ± 14.23	46	56	21.0 ± 13.51	14
		150 mg × 6	43.9 ± 14.41	41	58	20.6 ± 14.54	16
		placebo	43.7 ± 12.74	38	59	19.86 ± 12.20	12
A. Blauvelt	U.S.A	300 mg × 6	45.1 ± 12.57	38	54	18.0 ± 11.86	
		150 mg × 6	46.0 ± 15.09	40	51	20.4 ± 12.97	
		placebo	46.5 ± 14.14	39	57	20.2 ± 14.22	
Richard. G. Langley	Canada	300 mg × 6	44.9 ± 13.5	169	171	17.4 ± 11.1	
		150 mg × 6	44.9 ± 13.3	168	171	17.5 ± 12.0	
		placebo	45.4 ± 12,6	172	176	17.3 ± 12.4	
		300 mg × 6	44.5 ± 13.2	224	224	15.8 ± 12.3	
		150 mg × 6	44.5 ± 12.9	236	236	17.3 ± 12.2	
		placebo	44.1 ± 12.6	237	237	16.6 ± 11.6	
R.G. Langley	Canada						
Mamitaro. OHTSUKI	Japan	300 mg × 6	51.9 ± 11.77	26		15.6 ± 10.30	4
		150 mg × 6	48.2 ± 13.08	23		15.6 ± 10.41	5
		placebo	50.2 ± 13.62	23		14.1 ± 10.91	4

tors, for example, medical history, tolerability of therapies and potential side effects, and disease severity [6]. Despite the advances in systemic therapy, most patients with moderate to severe psoriasis are not satisfied with their treatment [7]. Previously, many researchers proved that various cytokines produced from keratinocytes, interleukin IL-23, IL-21, IL-22 and IL-17A and tumor necrosis factor-α are highly up-regulated in psoriatic skin. With the advance in the molecular biology, it provides the basis for development of new therapeutic approaches to psoriasis. There are several new emerging therapies targeting many cytokine pathways in psoriasis: the anti-TNF-α agents which is the biological era of psoriasis therapy including etanercept, adalimumab, and infliximab [8], the IL-17 inhibitors secukinumab, ixekizumab, and brodalumab [9], the IL-23 blocker tildrakizumab [10], other IL-23 pathway inhibitors in the pipeline including anti-p19 monoclonal antibody and apilimod (STA-5326), which interfere with IL-23 activity, as well as secukinumab (AIN-457), LY-2439821, and AMG-827, which exhibit their activity at other targets of the IL-23 pathway [11], the IL-12/IL-23 inhibitors ustekinumab [12], briakinumab [13] and guselkumaband, the small-molecule kinase inhibitors apremilast [14] (a phosphodiesterase-4 blocker) and tofacitinib [15] (a Janus kinase inhibitor) [16].

Emerging evidence suggests a central role of IL-17 in the pathogenesis of psoriasis, giving a rationale for using IL-17-blocking agents as therapeutics more effective than existing biologics [17]. There are three agents targeting IL-17 signaling being studied in Phase III clinical trials: secukinumab and ixekizumab (IL-17 neutralizing agents) [18], and brodalumab (IL-17 receptor antagonist) [19]. Preliminary results are highly promising for all anti-IL17 agents, creating significant expectations on this class of agents as the new effective therapeutic approach for the treatment of psoriasis [9].

Table 2. The general information of patients included in the mata-analysis

Study		IGA Score (n)			PASI (Mean ± SD)	UV therapy	Previous treatment (n)	
		Moderate	Severe	Very severe			Systemic therapy	Biologic therapy
Wolf gang. Hueber	150 mg	13	5	0	18.5 ± 8.7			
	placebo	11	5	1	18.3 ± 8.1			
K.A. PaPP	150 mg × 3	14	12	1	21.3 ± 9.41	18	15	8
	placebo	14	7	1	21.7 ± 8.53	16	16	8
P. Rich	150 mg × 1	28	35	3	19.9 ± 6.73	42	43	21
	150 mg × 3	64	62	12	20.8 ± 8.08	93	109	41
	150 mg × 4	65	62	6	19.9 ± 7.81	88	98	40
	placebo	26	34	7	20.5 ± 9.31	40	42	17
C. Paul	300 mg × 6	39	21		18.9 ± 6.37	30	34	15
	150 mg × 6	35	26		22.0 ± 8.85	31	34	15
	placebo	38	23		19.4 ± 6.7	29	33	13
A. Blauvelt	300 mg × 6	40	19			20	35	23
	150 mg × 6	37	22			39	45	28
	placebo	34	25			29	39	26
Richard. G. Langley	300 mg × 6	154	91		22.5 ± 9.2	128	163	70
	150 mg×6	161	84		22.3 ± 9.8	125	156	73
	placebo	151	97		21.4 ± 9.1	108	146	73
	300 mg × 6	203	124		23.9 ± 9.9	195	206	38
	150 mg × 6	206	121		23.7 ± 10.5	198	212	45
	placebo	202	124		24.1 ± 10.5	199	204	35
Mamitaro. OHTSUKI	300 mg × 6	16	13		26.7 ± 10.49	11	29	6
	150 mg × 6	18	11		28.2 ± 13.64	10	29	5
	placebo	22	7		21.4 ± 10.31	12	29	6

Secukinumab (Novartis Pharma AG, Basel, Switzerland) is a recombinant, high-affinity, fully human IgG1κ monoclonal antibody that selectively binds to IL-17A and neutralizes the bioactivity of this cytokine. Secukinumab has demonstrated efficacy in treating moderate to severe plaque psoriasis in phase 2 and phase 3 studies at dosage of 300 mg or 150 mg for subcutaneous injection. Therefore, we conducted a systematic review and meta-analysis on efficacy and safety of secukinumab at different doses in the treatment of moderate to severe plaque psoriasis.

The immune system, in particular T cell-mediated immune response, is crucial in the development of plaque psoriasis, which is characterized by extensive inflammation and altered keratinocyte differentiation. The relation between keratinocytes and immune cells, in particular T cells, is responsible for the two primary features of psoriasis, hyperproliferation and inflammation [20]. Th17 cells are supposed to be involved in various autoimmune diseases, such as rheumatoid arthritis, psoriasis, multiple sclerosis, and inflammatory bowel diseases [21, 22]. In 2014, Brown. G conducted a clinical study to assess the efficacy and safety of the anti-IL-17 biological therapies secukinumab, ixekizumab and brodalumab in patients. The results were as followings: By week 12, the proportion of patients reaching Psoriasis Area and Severity Index (PASI 75) was comparable among the most efficacious dosages of the different agents (secukinumab 82%, ixekizumab 83% and brodalumab 82%; $P < 0.001$ compared to placebo for all agents). The safety profiles of the agents were similar, with the most frequently reported adverse events of nasopharyngitis, upper respiratory infections and injection site reaction. The location of IL-17A relative to other cytokines in the inflammatory cascade, as well as its presence in dermal skin, has supported its investigation as a possible target in the treatment of psoriasis, and anti-

Table 3. The general information of patients included in the meta-analysis

Study	Research (mg)	Times	Total (N)	PASI75 (N)	PASI90 (N)	IGA (0-1) (N)
Wolf gang. Hueber	150	1	18	8	2	
	placebo		18	1	0	
K.A. PaPP						
	150	3	27	22		2
	placebo		22	2		2
P. Rich						
	150	1	66	6	2	3
	150	3	138	58	24	31
	150	4	133	72	42	49
	placebo		67	1	1	1
C. Paul						
	300	6	60	52	33	44
	150	6	61	44	24	32
	placebo		61	2	0	0
A. Blauvelt						
	300	6	59	45	35	41
	150	6	59	41	27	31
	placebo		59	0	0	0
Richard G. langley	300	6	245	200	145	160
	150	6	245	174	95	125
	placebo		248	11	3	6
	300	6	327	249	175	202
	150	6	326	219	137	167
	placebo		326	16	5	9
R.G. Langley						
	150	3	29	23	15	
	placebo		22	1	0	
Mamitaro. OHTSUKI	300	6	29	24	18	16
	150	6	29	25	16	16
	Placebo	6	29	2	0	10

IL17 biological therapy maybe a promising treatment [23, 24].

With many biological therapies having applied to clinical treatment, secukinumab may be the new and promising biological therapy for patients with psoriasis. Many scientists have set sights on secukinumab and performed a great deal of clinical studies on it. This paper focuses mainly on the efficacy and safety of the different doses of secukinumab. The results showed that secukinumab could improve the skin condition and there were no significant adverse effects. The meta-analysis may be controversial due to the limited availability of references. However, it is the first meta-analysis on secukinumab and needs to include more clinical studies in it to better clarify the efficacy and safety of this agent.

Materials and methods

Identification of materials

Electronic searches of the Pubmed, the Cochrane Library, MEDLINE, EMBASE and Wanfang Database for all publications about secukinumab were performed. We used the keywords and subject terms: ("psoriasis" and "psoriatic") and ("secukinumab" or "AIN-457"). The following criteria were used to select the eligible studies: (1) male and female subjects aged ≥ 18 years; (2) plaque psoriasis for ≥ 6months; baseline moderate-to-severe disease (psoriasis area and severity index [PASI] score ≥ 12, modified 2011 static 5-point investigator's global assessment [IGA mod 2011 0/1] 12 score ≥ 3, and body surface area [BSA] involvement ≥ 10%); (3) disease inadequately controlled by systemic topical treatments, phototherapy such an NB-UVB, or previous systemic therapy such as acitretin, cyclosporine, and methotrexate; (4) the pivotal exclusion criteria were forms of psoriasis other than chronic plaque, continuous use of prohibited psoriasis treatments or prohibited non-psoriasis medications, or previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or the IL-17 receptor.

Data extraction

Data retrieved from the studies included the first author's name, country, age and gender of patients, duration of psoriasis and patients with psoriatic arthritis (**Tables 1**, **2**). The primary endpoints were the PASI 75 and PASI 90 response rates, proportion of participants with

Table 4. The adverse effects of patients included in the meta-analysis

Study	Total (N)	Research	AE	SAE	Death	Discontinuations due to AE	Infections	Headache	Hypertension	Nasopharyngitics	Prutitus	Backpain
Wolf gang. Hueber	18	150 mg	9	1	0	0	5	1	2		0	
	18	placebo	8	0	0	0	3	1	1			0
K.A. PaPP												
	27	150 mg	24	0	0	1		1	2	6	1	1
	22	placebo	16	2	1	0		0	0	2	3	0
P. Rich												
	66	150 mg	41	3	0	1	14	6	3	8		0
	138	150 mg	91	3	0	0	56	8	1	31		2
	133	150 mg	89	6	0	3	45	11	2	30		3
	67	placebo	47	1	0	1	26	3	1	12		1
C. Paul												
	60	300 mg	42	1	0	0		3	1	19	5	
	61	150 mg	39	3	0	0		5	3	14	1	
	61	placebo	33	1	0	1		3	4	10	2	
A. Blauvel	59	300 mg	30	3	0	1		0		3		3
	59	150 mg	34	0	0	0		4		3		0
	59	placebo	28	1	0	1		3		5		0
Richard G. langley	326	300 mg	181	4	0	4	87	30		35	8	8
	327	150 mg	191	7	0	2	101	16		45	12	8
	323	placebo	186	3	0	6	79	23		36	8	9
R.G. Langley												
	29	150 mg	24	0	0	1		1	2	4	3	1
	22	placebo	16	2	1	0		0	0	2	2	0
Mamitaro. OHTSUKI												
	29	300 mg	14	0	0	0				5	1	
	29	150 mg	16	2	0	2				4	1	
	29	placebo	12	0	0	1				5	2	

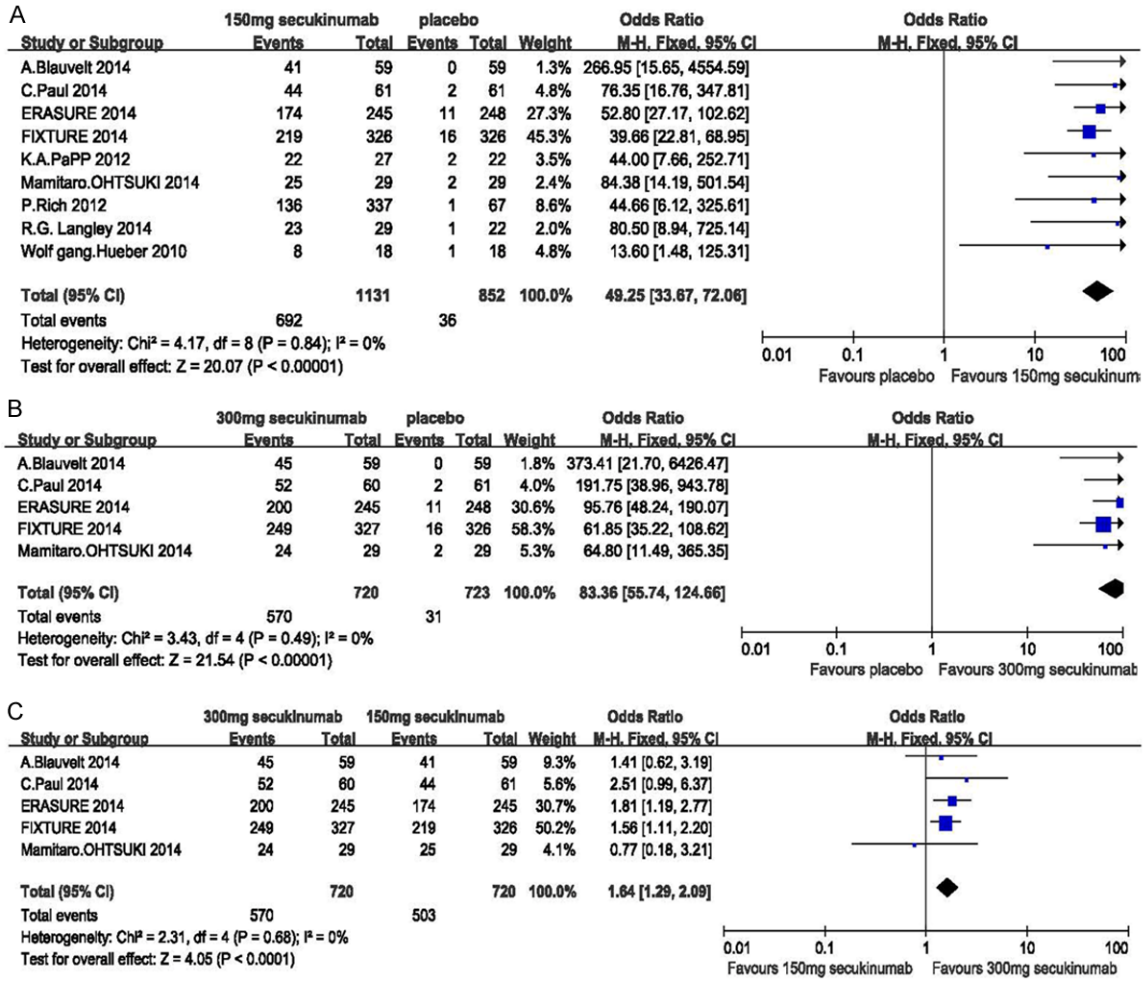

Figure 1. Meta-analysis of PASI75 comparing the secukinumab groups with placebo at week 12. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of PASI75 comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of PASI75 comparing the secukinumab300 mg groups with placebo at week 12. C. Meta-analysis of PASI75 comparing the secukinumab300 mg groups with secukinumab150 mg at week 12.

75% and 90% decrease in the Psoriasis Area and Severity Index (PASI). And the PASI 75 has been shown to correspond with good patient satisfaction with respect to their treatment response and has recently been adopted as a standard treatment goal by a European expert consensus group [25]. As we know, PASI 75 response meets therapeutic expectations in most patients, and is used very commonly by clinicians in evaluating the severity and prognosis of patients with psoriasis. PASI 90 response or better has a significantly higher impact on DLQI improvement and is associated with significantly higher DLQI = 0-1 response rates. The new anti-IL17 drug in clinical practice has the promise of achieving PASI 90 response or better in the majority of patients [26]. We have retrieved the IGA score and PASI score of patients included in the meta-analysis (**Table 3**). Since we needed to assess the safety of this biological drug, we collected the number of patients who had adverse effects after receiving subcutaneous injection of secukinumab (**Table 4**). Finally, the meta-analysis is with 1,361 patients on secukinumab treatment and 1,852 patients on placebo treatment.

Statistical methods

We connected data using Review Manager 5 and showed dischotmous outcome as odds ratio (OR), using chi-square test to assess the extent of inconsistency, the size of test a = 0.1. Data analysis was performed using the fixed-

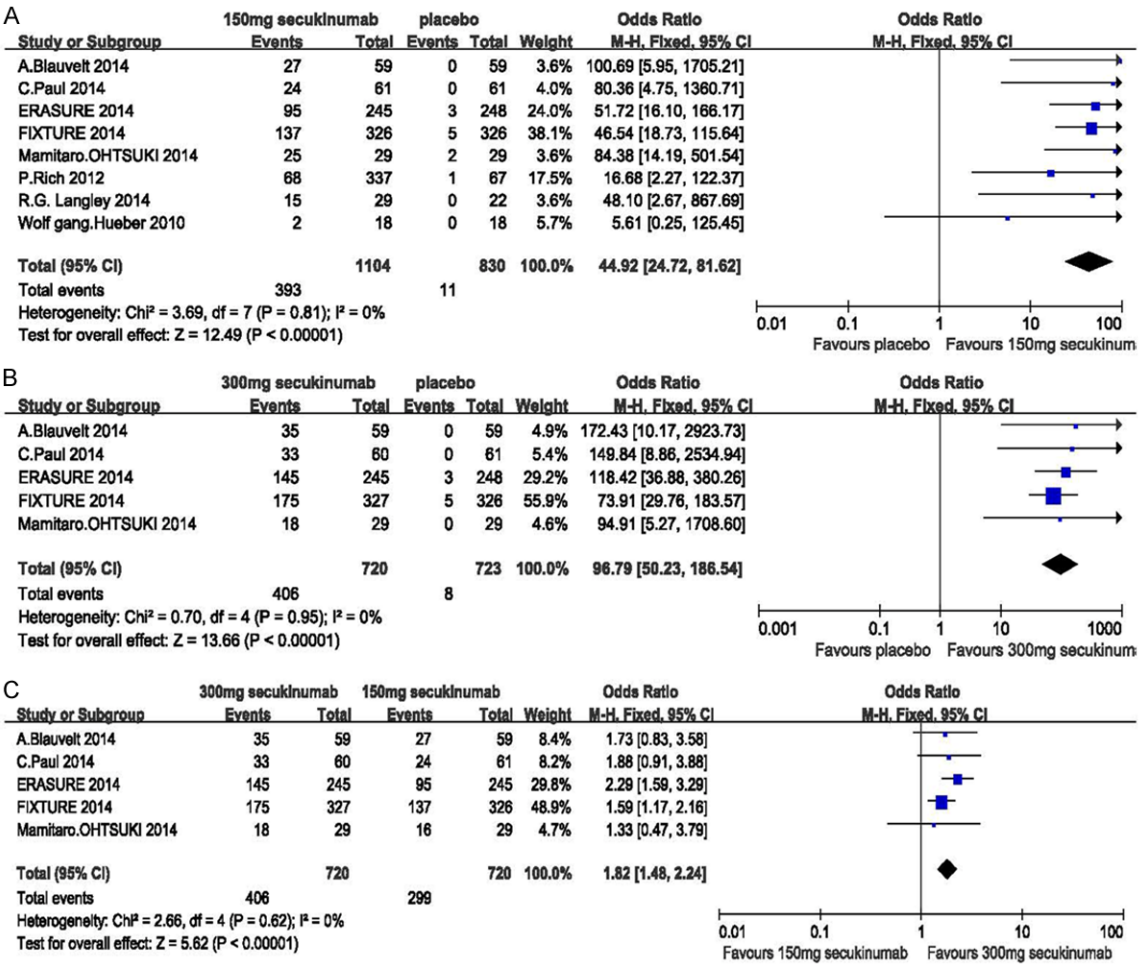

Figure 2. Meta-analysis of PASI90 comparing the secukinumab groups with placebo at week 12. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of PASI90 comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of PASI90 comparing the secukinumab300 mg groups with placebo at week 12. C. Meta-analysis of PASI90 comparing the secukinumab300 mg groups with secukinumab150 mg at week 12.

effect mode with no significant heterogeneity or using a random-effect mode with significant heterogeneity. U test (z test) was performed to assess the combined statistical outcomes. For better understanding of the efficacy of this biological therapy, three indicators (PASI 75, PASI 90 and IGA mod 2011 0/1) were used to analysis the efficacy. Another important indicator was the safety of secukinumab, so we collected three common adverse effects to assess the safety of secukinumab. Eventually, we summarized three common adverse effects such as headache, hypertension and nasopharyngitis. To get a more comprehensive assessment of efficacy and safety of secukinumab, two comparable models were used: (1) 150 mg secukinumab group versus placebo group; (2) 300 mg secukinumab group versus placebo group. The I^2 statistic to quantify the proportion of the total variation due to heterogeneity was calculated, and an I^2 value of more than 50% was interpreted as significant heterogeneity among studies. When the effects were assumed to be homogenous, the fixed-effects model was used. If the significant heterogeneity was presented, the random-effects model was used.

Results

Literature search

A total of eight documents met the inclusion criteria, with 1,361 patients receiving secukinumab treatment. Two hundreds and eight articles were found, as follows:

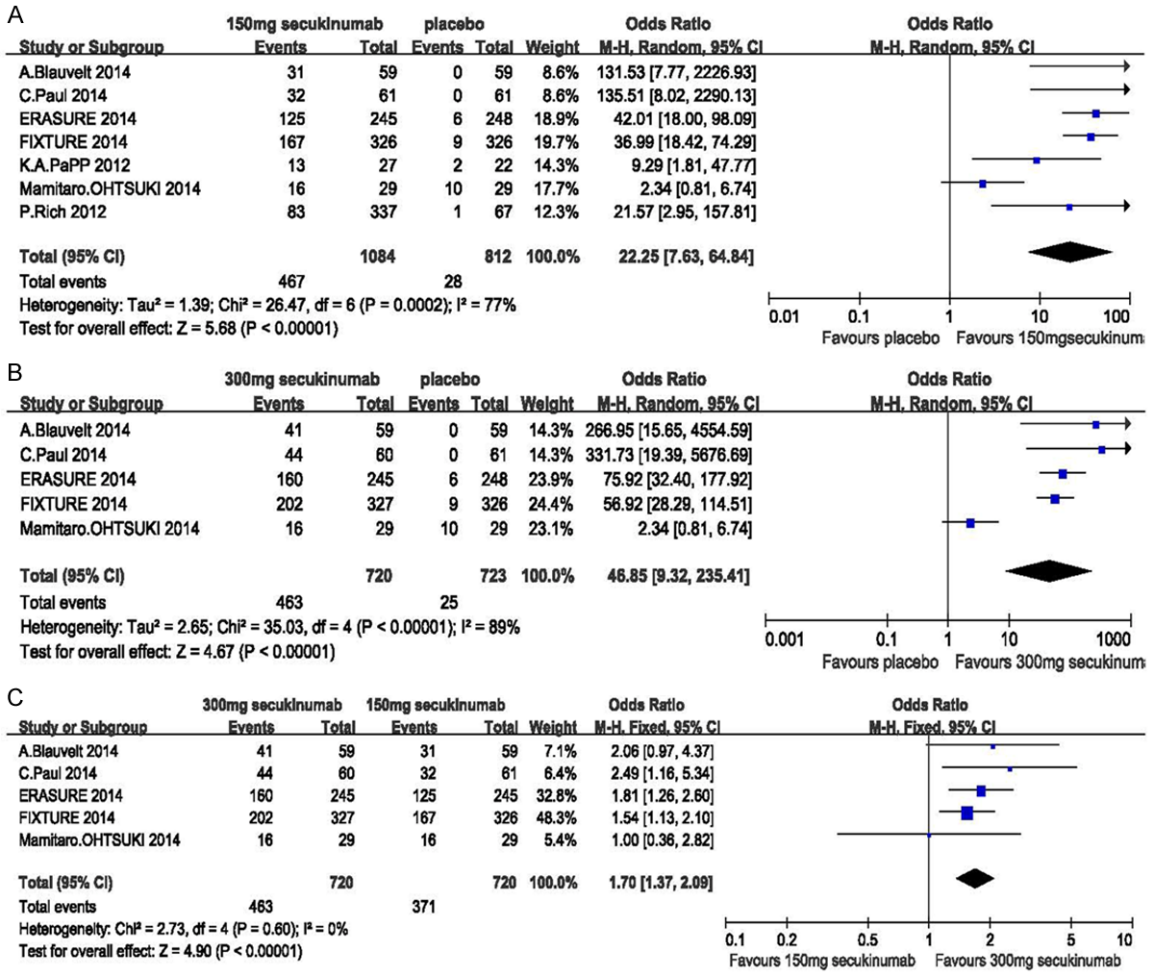

Figure 3. Meta-analysis of IGA comparing the secukinumab groups with placebo at week 12. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of IGA comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of IGA comparing the secukinumab300 mg groups with placebo at week 12. C. Meta-analysis of IGA comparing the secukinumab300 mg groups with secukinumab150 mg at week 12.

Pubmed, n = 130; EMBASE, n = 0; Cochrane Library, n = 25; Medline, n = 0; ENDLINE, n = 0; and Wanfang Database, n = 53. Eight eligible studies published between 1989 and 2014 were finally identified according to our predefined selection criteria (**Figure 10**).

Characteristics of studies

All studies included in the meta-analysis are randomized double-blinded place-controlled studies. Wolfgang Hueber [27] and colleagues treated 60 patients (including those with psoriasis, rheumatoid arthritis and uveitis) with secukinumab at different dosages and found no serious adverse effects. In the psoriasis group, there were 18 patients receiving secukinumab and 18 patients receiving placebo. After 12 weeks, data about all PASI scores and adverse effects were collected through the graphs.

K.A.PaPP [28] and colleagues performed a clinical study at 2012. The patients were randomized at the ratio of 1:1:1:1 to receive subcutaneous doses of placebo (n = 22) or secukinumab [1 × 25 mg (n = 29), 3 × 25 mg (n = 26), 3 × 75 mg (n = 21) or 3 × 150 mg (n = 27)] at 0, 4 and 8 weeks.

In the study by P. Rich, a total of 404 patients were randomized to receive subcutaneously placebo (n = 67) or one of the three secukinamab 150 mg induction regimens: single (week 0; n =

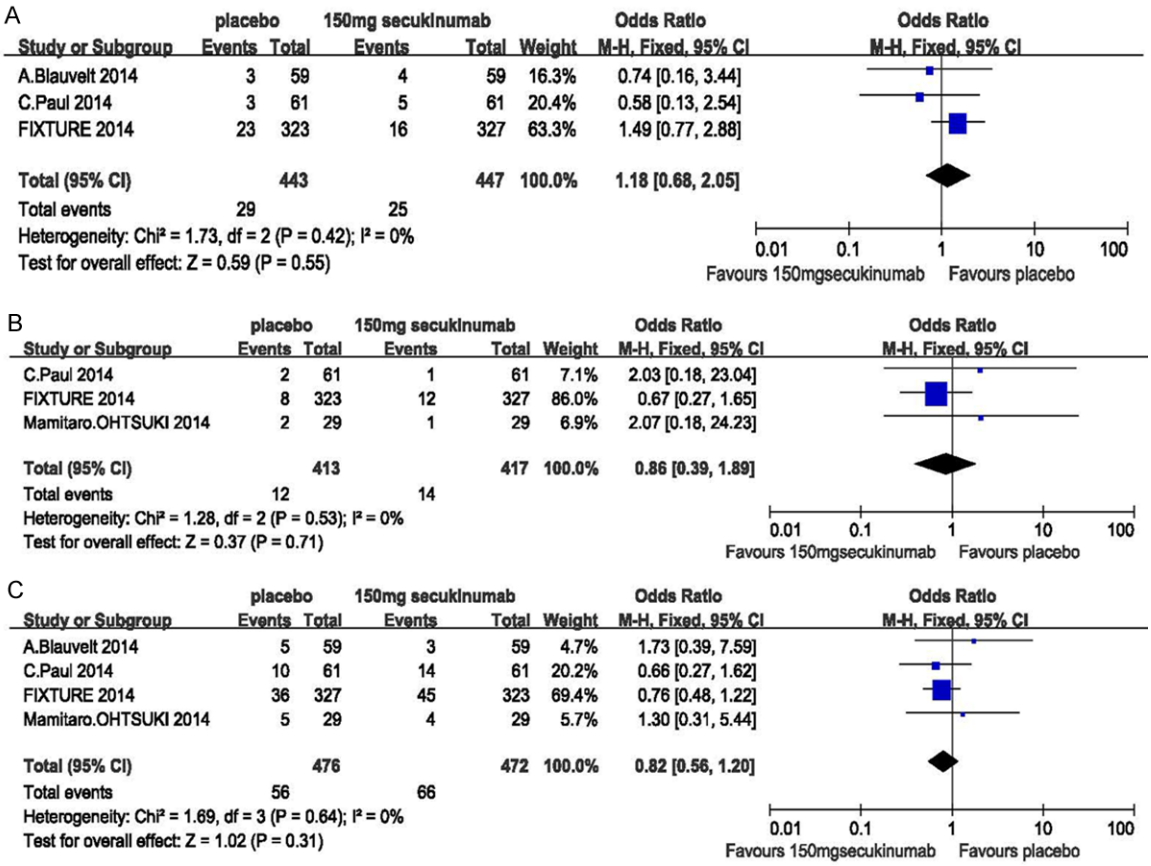

Figure 4. Meta-analysis of adverse effects comparing the secukinumab150 mg groups with placebo at week 12. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of Headache comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of pruritus comparing the secukinumab150 mg groups with placebo at week 12. C. Meta-analysis of nasopharyngitis comparing the secukinumab150 mg groups with placebo at week 12.

66), early (week 0, 1, 2 and 4; n = 133) and monthly (week 0, 4 and 8; n = 138 patients). The primary endpoint was ≥ 75% improvement from baseline in Psoriasis Area and Severity Index score (PASI 75) at week 12. The study also collected adverse effects of patients included in the experiment.

In the study by C. Paul, this phase 3 trial randomized subjects with moderate to severe plaque psoriasis to secukinumab 300 mg, 150 mg or placebo self-injection once weekly to week 4, then every 4 weeks at week 12. Co-primary endpoints at week 12 were ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and clear skin by investigator's global assessment 2011 modified version (IGA mod 2011 0/1).

In the study by A. Blauvelt [29], subjects in this phase 3 trial were randomized 1:1:1 to secukinumab 300 mg or 150 mg or matching placebo. Co-primary endpoints were met at week 12, with demonstration of superiority for each secukinumab dose over placebo at Week 12 (PASI 75:75.9%, 69.5%, and 0% for secukinumab 300 mg and 150 mg and placebo respectively; IGA 2011 mod score 0-1: 69.0%, 52.5%, and 0%, respectively; $P < 0.0001$ for all comparisons vs. placebo).

In the study by Richard G. Langley, the research included two parts, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis). The study randomly assigned 738 patients (in the ERASURE study) and 1,306 patients (in the FIXTURE study) to subcutaneous secukinumab at a dose of 300 mg or 150 mg (administered once week-

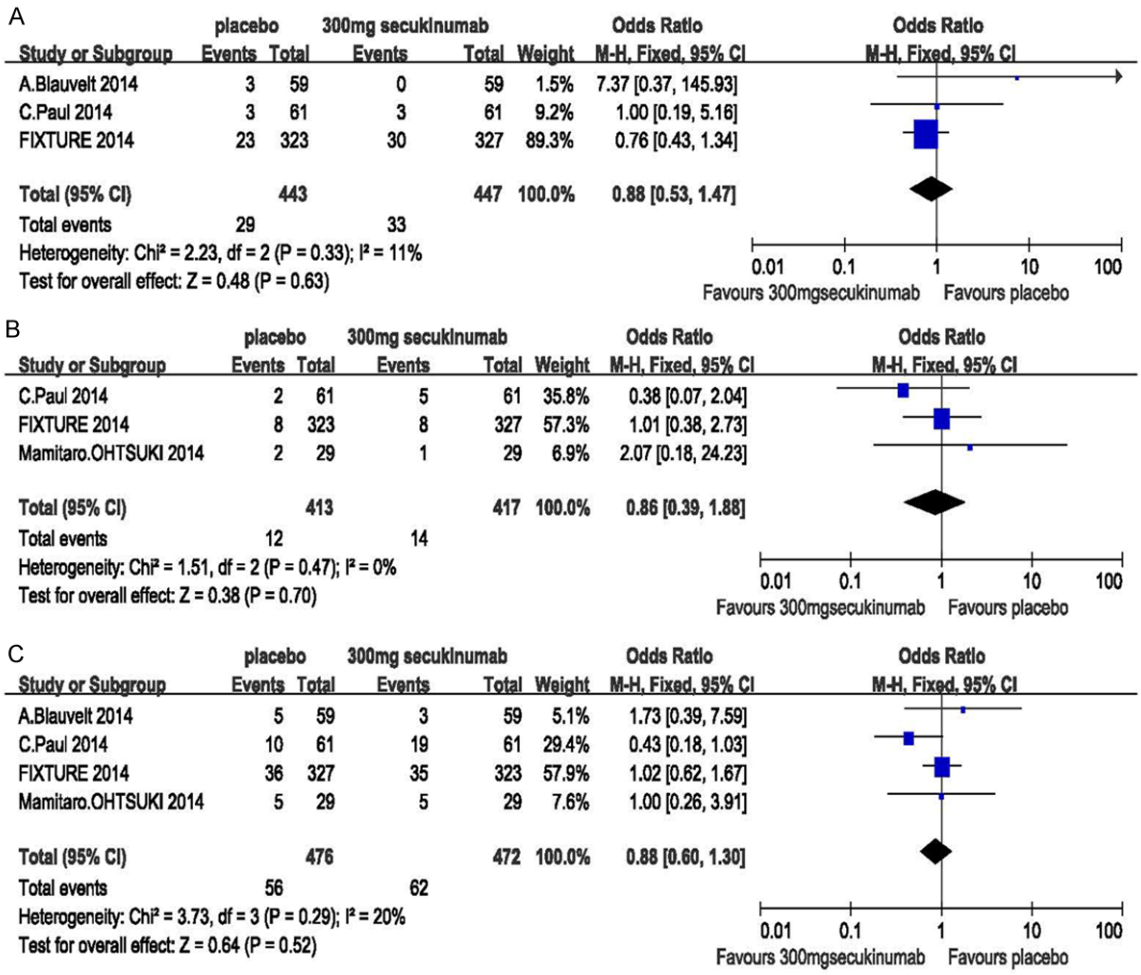

Figure 5. Meta-analysis of adverse effects comparing the secukinumab300 mg groups with placebo at week 12. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of Headache comparing the secukinumab300 mg groups with placebo at week 12. B. Meta-analysis of pruritus comparing the secukinumab300 mg groups with placebo at week 12. C. Meta-analysis of nasopharyngitis comparing the secukinumab300 mg groups with placebo at week 12.

ly for 5 weeks, then every 4 weeks), placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg (administered twice weekly for 12 weeks, then once weekly). Due to the large sample size, we divided the trial into two parts to complete the meta-analysis.

In the study by R. G. Langley, this was a double-blind, parallel group, placebo-controlled, phase 2 study in which 125 patients were randomized to subcutaneous doses of placebo (n = 22) or secukinumab (1 × 25 mg [n = 29], 3 × 25 mg [n = 26], 3 × 75 mg [n = 21], 3 × 150 mg [n = 27]) at weeks 0, 4, and 8.

In the study by Mamitaro Ohtsuki [1], eligible Japanese patients were randomized (1:1:1) to secukinumab 300 mg, secukinumab 150 mg, or placebo, with all doses given once weekly at baseline and at weeks 1, 2, 3, and 4, then every 4 weeks until week 48. Patients randomized to secukinumab groups received either of the two 150 mg subcutaneous secukinumab injections (i.e., 300 mg) or one 150 mg injection plus one placebo injection.

At last, we collected data which included PASI 75, PASI 90 and IGA 2011 mod score 0-1 about 150 mg secukinumab, secukinumab 300 mg and placebo (**Table 3**). Among all the studies, after using the biological therapy, the common adverse effects (**Table 4**) included infections, headache, hypertension, nasopharyngitis and pruritus. The meta-analysis about headache,

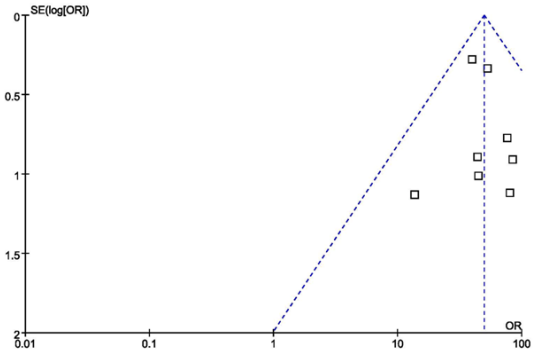

Figure 6. Funnel plots of PASI75.

nasopharyngitis and pruritus were presented as followings.

Meta-analysis

Efficacy of secukinumab injection at week 12

Secukinumab groups vs. placebo groups: PASI 75: Eight references were included in the meta-analysis. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. The outcome shows that on PASI75, the secukinumab 150 mg group had more benefit (OR = 49.25, 95% CI [33.67, 72.06]) compared with the placebo group (P < 0.00001) (**Figure 1A**). Four references were included in the meta-analysis of secukinumab 300 mg and placebo. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. The result was that on PASI75, the secukinumab 300 mg group had more benefit (OR = 83.36, 95% CI [55.74, 124.60]) compared with the placebo group (**Figure 1B**).

PASI 90: Seven references were included in the meta-analysis of secukinumab 150 mg vs. placebo. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. It was shown that on PASI90, the secukinumab 150 mg group had more benefit (OR = 44.92, 95% CI [24.72, 81.62]) compared with the placebo group (P < 0.00001) (**Figure 2A**). Four references were included in the meta-analysis of secukinumab 300 mg and placebo. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. It was shown that on PASI 90, the secukinumab 300 mg group had more benefit (OR = 96.79, 95% CI [50.23, 186.54]) compared with the placebo group (**Figure 2B**).

IGA mod 2011 0/1: As heterogeneity was detected among the included trials, a random-effect model was used to perform meta-analysis. It was shown that on IGA mod 2011 0/1, the secukinumab 150 mg group had more benefit (OR = 22.25, 95% CI [7.63, 64.84]) compared with the placebo group (P < 0.00001) (**Figure3A**). As heterogeneity was detected among the included trials, a random-effect model was used to perform the meta-analysis. It was shown that on IGA mod 2011 0/1, the secukinumab 300 mg group had more benefit (OR = 46.85, 95% CI [9.32, 235.41]) compared with the placebo group (P < 0.00001) (**Figure 3B**).

Secukinumab 300 mg compared with secukinumab 150 mg: PASI 75: Four references were included in the meta-analysis. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. The results showed that the secukinumab 300 mg group had more benefit than the secukinumab 150 mg group (OR = 1.64, 95% CI [1.29, 2.09]) (P < 0.00001) (**Figure 1C**).

PASI 90: Four references were included in the meta-analysis. Where there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the corresponding 95% CIs. The results showed that the secukinumab 300 mg group had more benefit than the secukinumab 150 mg group (OR = 1.82, 95% CI [1.48, 2.24]) (P < 0.00001) (**Figure 2C**).

IGA mod 2011 0/1: As no heterogeneity was detected among the included trials, a fixed-effect model was used to perform the meta-analysis. It was shown that on IGA mod 2011 0/1, the secukinumab 300 mg group had more benefit (OR = 1.70, 95% CI [1.37, 2.09]) compared with the secukinumab 150 mg group (P < 0.00001) (**Figure 3C**).

Adverse effects of secukinumab at 12 weeks

As is shown in **Table 4**, we have summarized the common adverse effects including infec-

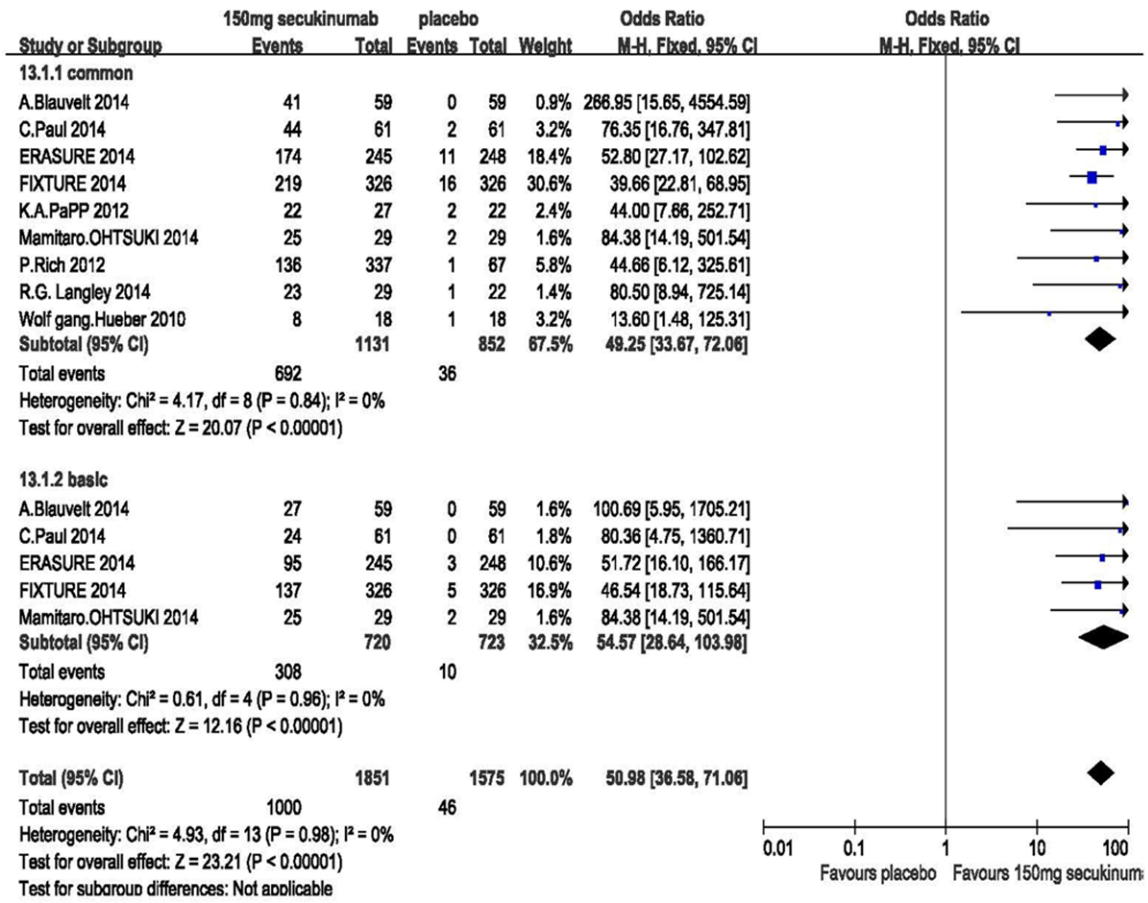

Figure 7. Subgroup analysis of PASI75 among the secukinumab150 mg groups. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of common treatment of PASI75 comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of basic treatment of PASI75 comparing the secukinumab150 mg groups with placebo at week 12.

tions, headache, hypertension, nasopharyngitis, pruritus and back pain. The proportion of patients with serious adverse effects reached 2%. There were 22 patients who could not finish the trials. There were two patients who died in the trial. In the secukinumab 150 mg group, there were 63% of patients experiencing the adverse effects. In the secukinumab 300 mg group, there were 57% of patients experiencing the adverse effects.

Adverse effects of the secukinumab groups compared with the placebo group: Headache: The results showed that there was no significant difference in the incidence of headache between the secukinumab 150 mg group and the placebo group (OR = 1.18, 95% CI [0.68, 2.05], P = 0.55) (**Figure 4A**). The results showed that there was no significant difference in the incidence of headache between the secukinumab 300 mg group and the placebo group (OR = 0.88, 95% CI [0.53, 1.47], P = 0.63) (**Figure 5A**).

Pruritus: In the comparison of secukinumab 150 mg to placebo, 3 studies were included. Since $I^2 = 0$, we used the fixed-effect model to analysis the data, and the results showed that there was no statistical significance (OR = 0.86, 95% CI [0.39, 1.89], P = 0.41) (**Figure 4B**). In the comparison of secukinumab 300 mg to placebo, there was no significant difference in the incidence of headache between the secukinumab 300 mg group and the placebo group (OR = 0.86, 95% CI [0.39, 1.88], P = 0.70) (**Figure 5B**).

Nasopharyngitis: While there was no heterogeneity among the references, we used the fixed-effects model to calculate pooled ORs with the

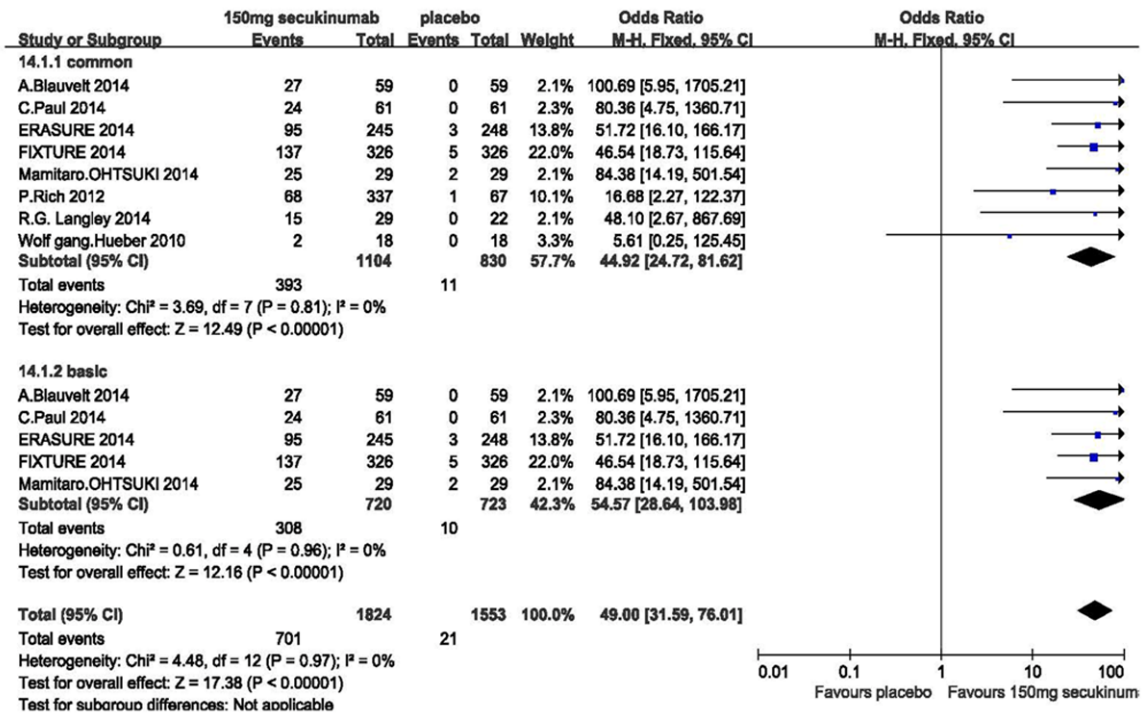

Figure 8. Subgroup analysis of PASI90 among the secukinumab150 mg groups. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of common treatment of PASI90 comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of basic treatment of PASI90 comparing the secukinumab150 mg groups with placebo at week 12.

corresponding 95% CIs. The results showed that there was no significant difference between the secukinumab group and the placebo group (**Figure 4C** (OR = 10.82, 95% CI [0.56, 1.20, P = 0.31])) (**Figure 5C** (OR = 0.88, 95% CI [0.60, 1.30], P = 0.52)).

Publication bias

Funnel plots were used to evaluate the possibility of publication bias, indicating no evidence of publication bias (**Figure 6**).

Discussion

The common treatment for moderate to severe psoriasis is usually systemic and may involve biologic or non-biologic drugs [30]. Now scientists set their sights on the biological therapies. Our meta-analysis showed that the secukinumab 300 mg dose had greater benefit than the 150 mg dose at week 12, and through our meta-analysis, we found that when compared to placebo, all biologics demonstrated superior efficacy. Secukinumab also showed an acceptable safety and tolerability profile for both doses at week 12. Finally we can make the conclusion that secukinumab is effective and safe and our meta-analysis provides the information that is useful both for clinicians and for managers in the decision-making processes.

Secukinumab, a novel, selective anti-IL-17A targeted therapy, improves symptoms rapidly and significantly. Through our systematic review and meta-analysis, the results showed a trend that the secukinumab 300 mg group was better than the secukinumab 150 mg group, considering strictly PASI response and IGA mod 2011 0/1 as the co-primary endpoints for moderate to severe psoriasis, after 12 weeks of treatment. However, in the study by Mamitaro Ohtsuki, PASI 75 and IGA mod 2011 0/1 responses at week 12 were superior for secukinumab 300 mg (82.8% and 55.2%, respectively) and 150 mg (86.2% and 55.2%, respectively) over placebo (6.9% and 3.4%, respectively; P < 0.0001 for all). Greater than 90% improvement in PASI (PASI 90) was also seen with secukinumab 300 mg (62.1%) and 150 mg (55.2%), superior over placebo (0.0%) at week 12 (P < 0.0001 for both). The results

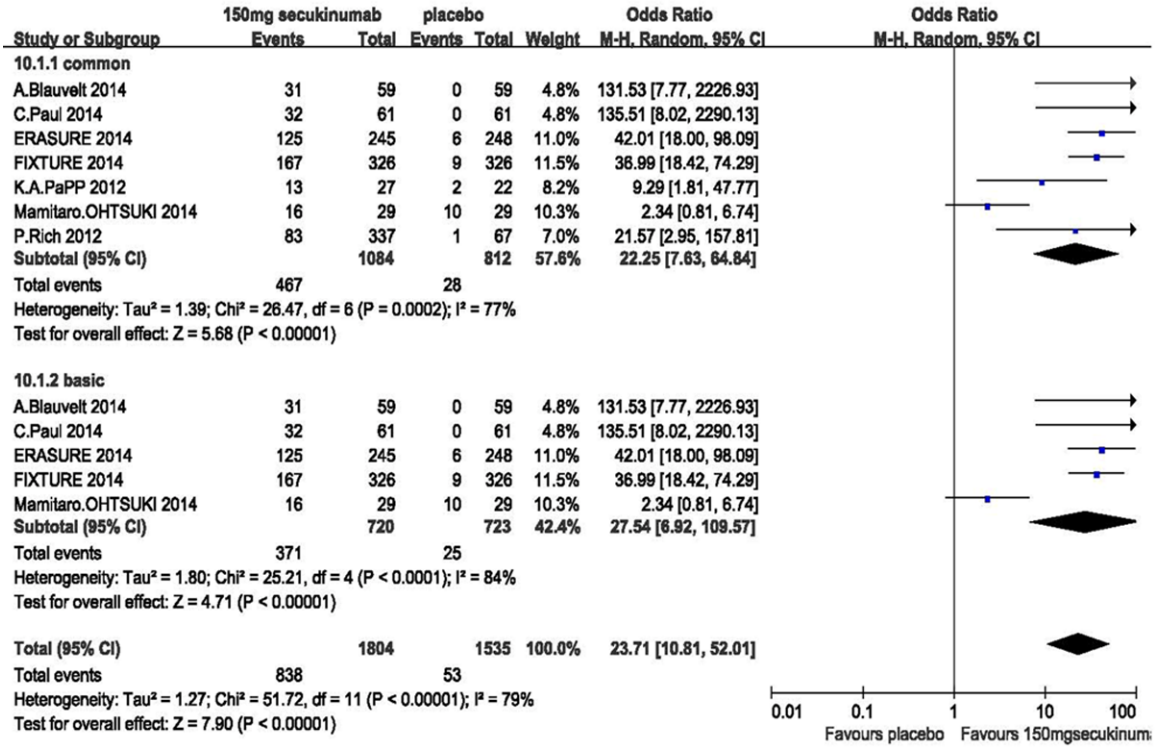

Figure 9. Subgroup analysis of IGA among the secukinumab150 mg groups. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). A. Meta-analysis of common treatment of IGA comparing the secukinumab150 mg groups with placebo at week 12. B. Meta-analysis of basic treatment of IGA comparing the secukinumab150 mg groups with placebo at week 12.

showed that the number of patients treated with secukinumab 150 mg achieving PASI 75 was higher than that with secukinumab 300 mg, different from the results of our meta-analysis. Considering the overall efficacy, the results favored the use of the 300 mg dose. Reason may be that this study is aimed at the Asian race, unlike other studies mainly conducted in white people and more Asian patients are needed to be included in the clinical research of this promising biological drug. At last, to determine the efficacy of secukinumab when compared with other biological therapies, further RCTs are needed to prove it. Since psoriasis is a chronic disease, results of long term follow-up are needed to better understand the efficacy and safety of these drugs. Unfortunately, not all RCTs included in the meta-analysis have extensive follow-up research. To evaluate that, we suggest conducting more systematic review of studies evaluating the maintenance of PASI 75 or 90 or IGA mod 2011 0/1 through an extensive follow-up research.

There were no statistically significant differences in the incidence of serious adverse events and infections between the biological agent and placebo. Common adverse effects included infections, headaches, hypertensions, nasopharyngitis, pruritus and back pain. Serious adverse effects included acute myocardial infarction, neoplasms, viral gastroenteritis, transient ischaemic attack and psoriatic arthropathy. The meta-analysis showed there was no statistically significant difference between the secukinumab groups and the placebo group. It was demonstrated that secukinumab was well tolerated, with an overall good safety profile, suggesting that targeted blockade of IL-17A does not result in toxicities in specific target organs or the immune system over the short term. These findings must be corroborated by larger-scale, long-term studies.

Several limitations should be considered when interpreting the findings from this meta-analysis. Currently, there were only eight case-control studies published investigating the efficacy of secukinumab in treating psoriasis, and there are not any studies were published investigating the biological therapy in Africans. In the

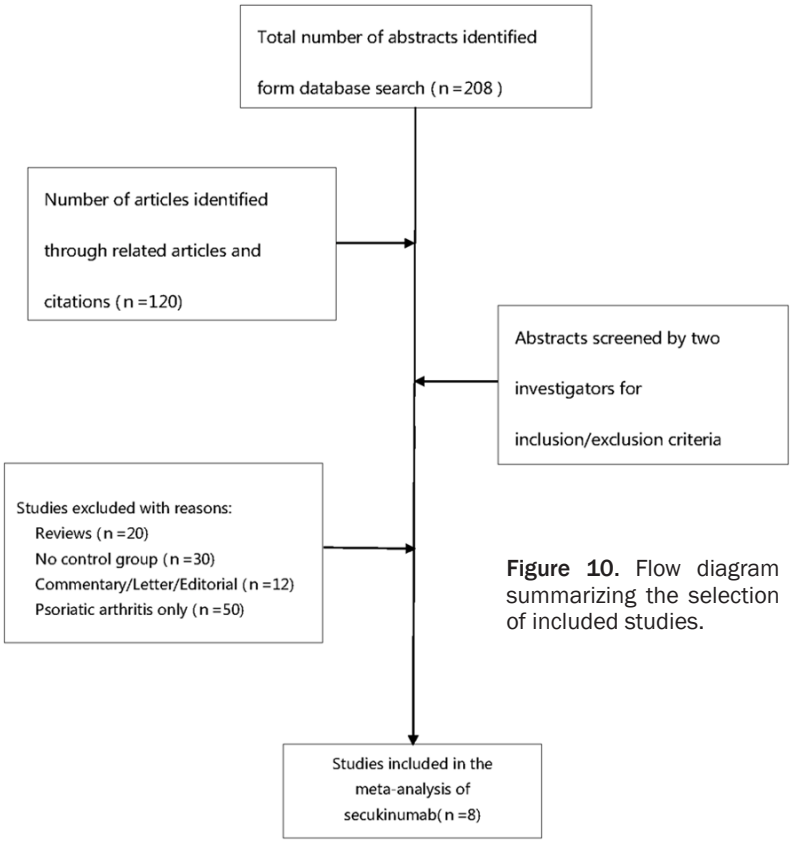

Figure 10. Flow diagram summarizing the selection of included studies.

study by Mamitaro OHTSUK, there were only eighty seven Japanese patients. Of all the participants included in the meta-analysis, the white accounted for a large proportion. The limited number of eligible studies gave a relatively small sample size, and further resulted in poor validation. Therefore, more well-designed studies with large sample size are needed to further identify the association among the Asians and the Africans.

Another limitation in the meta-analysis was that in the secukinumab 150 mg group, the total frequency of administration from the baseline to week 12 was different. In the study by C. Paul, A. Blauvelt, Richard G. Langley and Mamitaro OHTSUK, the frequency of using secukinumab 150 mg and secukinumab 300 mg was the same, with all doses given once weekly at baseline and at weeks 1, 2, 3, and 4, then every 4 weeks until week 12. Finally we have done the subgroup analysis of the PASI 75 (**Figure 7**), PASI 90 (**Figure 8**) and IGA mod 2011 0/1 (**Figure 9**) in patients using secukinumab 150 mg. The results showed that there was no difference when the frequency of administration was different.

Although the references included are of high quality, the number of patients in the trial by Richard G. Langley account for a significant proportion. This study of high quality was published in the *New England Journal of Medicine*, which assigned 738 patients (in the ERASURE study) and 1,306 patients (in the FIXTURE study). Considering the weight of the references included, the meta-analysis on secukinumab may lose its significance when the paper of Richard G. Langley is excluded.

Finally, even though this meta-analysis is controversial, it is the first meta-analysis on the efficacy and safety of the new biological therapy secukinumab. This paper may give evidences and guidance for the future clinical application and more randomized controlled trials of secukinumab are needed.

Conclusion

In conclusion, secukinumab 150 mg and 300 mg administered subcutaneously meet the primary endpoints of PASI 75/90 response rates and IGA 2011 mod score 0/1 after 12 weeks of treatment, demonstrating efficacy in the treatment of moderate to severe plaque psoriasis. And secukinumab 300 mg has more advantages than secukinumab 150 mg. Compared with placebo, there are no significant adverse effects in the secukinumab groups, demonstrating safety in the treatment of moderate to severe plaque psoriasis.

Acknowledgements

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Disclosure of conflict of interest

None.

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