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Original Article

Comparative Efficacy and Safety of Secukinumab and Adalimumab in Patients with Active Ankylosing Spondylitis: A Bayesian Network Meta-analysis of Randomized Controlled Trials

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Objective. This study assessed the efficacy and safety of secukinumab and adalimumab in patients with active ankylosing spondylitis (AS). **Methods.** A Bayesian network meta-analysis was performed with direct and indirect data collected from randomized controlled trials (RCTs) of efficacy and safety of secukinumab 75 mg, 150 mg and adalimumab 40 mg in patients with active AS. **Results.** Five RCTs (1,483 patients) met the inclusion criteria. The Assessment in Spondyloarthritis International Society response criteria of ≥20% (ASAS20) response rate was significantly higher in the adalimumab 40 mg (Odds ratio [OR], 4.26; 95% credible interval [CrI], 2.09～8.08), secukinumab 150 mg (OR, 3.35; 95% CrI, 1.73～6.56), and 75 mg dose (OR, 2.44; 95% CrI, 1.06～5.05) than with placebo. The ranking probability based on the surface under the cumulative ranking curve (SUCRA) indicated that adalimumab 40 mg had the highest probability of being the best treatment for achieving an ASAS20 response (SUCRA = 0.8753), followed by secukinumab 150 mg (SUCRA = 0.7051), secukinumab 75 mg (SUCRA = 0.4113), and placebo (SUCRA = 0.0083). The ASAS40 response rate distribution pattern was similar to the ASAS20 response rate. However, the number of serious adverse events did not differ significantly among the treatment options. **Conclusion.** Secukinumab and adalimumab were effective for the treatment of active AS without causing a significant risk of serious adverse events. **(J Rheum Dis 2017;24:211-219)**

Key Words. Secukinumab, Adalimumab, Ankylosing spondylitis, Network meta-analysis

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by entheses and inflammation in the spinal and sacroiliac joints, which initially causes bone and joint erosion, and eventually leads to new bone formation, syndesmophytes, and ankylosis, resulting in progressive structural damage, disability, and a reduced quality of life [1,2].

Drugs used for the treatment of AS include non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs. However, these drugs are often not effective for the treatment of AS [3]. Previous studies have shown that tumor necrosis factor (TNF) messenger RNA increases in the sacroiliac joints of AS patients. TNF plays a key role in the inflammatory activity associated with AS [4]. For patients with inadequate response despite conventional treatment, the anti-TNF therapy is currently recommended [3]. Studies have shown that anti-TNF therapy fails to achieve adequate disease control or has unacceptable side effects in approximately 40% of patients [5]. However, there are no approved alternative therapies available. Therefore, there is an unmet need for new types of drugs with new mechanisms of action. Recent studies have suggested that interleukin-17A may play in important role in the in-

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flammatory responses associated with AS. IL-17A and its receptor are expressed in target tissues in patients with AS and can mediate biological functions leading to joint and entheseal inflammation, damage, and tissue remodeling [6]. Secukinumab is a human, high-affinity, anti-IL-17A monoclonal antibody [7]. Clinical trials have attempted to evaluate the efficacy and safety of secukinumab in patients with active AS [8,9]. Previous trials have shown that secukinumab may be effective in the treatment of active AS patients, and may have a manageable safety profile [8,9]. Conversely, adalimumab is the first human, anti-TNF monoclonal antibody of proven efficacy and safety in the treatment of active AS, and is injected subcutaneously every other week. Adalimumab is the most widely used agent, and has shown comparable efficacy with other TNF inhibitors in the treatment of active AS [10-12].

In order to make an informed decision on which of these therapies is more effective and safer, studies that compare their efficacy and safety profile are necessary. However, studies making direct comparisons on the safety and efficacy between secukinumab and adalimumab are lacking. A network meta-analyses can combine direct and indirect data derived from relative treatment effects across a network of randomized controlled trials (RCTs), and thus can assess the effectiveness of multiple interventions even in the absence of studies directly comparing these therapies [13]. Recently, two network meta-analysis papers on biologic agents in patients with active AS have been published [14,15]. However, one meta-analysis study did not include the latest study on secukinumab for treatment of AS [14], and the other did not consider dosage of secukinumab as well as it did not include the latest studies [15]. In addition, there have been no comparative data on safety of biologics for treatment of AS. Using a network meta-analysis, the present study aimed to compare the efficacy and safety of secukinumab and adalimumab to a placebo in patients with active AS.

MATERIALS AND METHODS

Identification of eligible studies and data collection

We performed an exhaustive literature search using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register to identify available articles (up to January 2017) on the efficacy and safety of secukinumab and adalimumab in patients with active AS. The key words and subject terms used in the search included "secukinumab," "adalimumab," and "ankylosing spondylitis." All references in the studies were reviewed to identify additional works not included in the electronic databases. RCTs were included if (1) the study compared secukinumab or adalimumab with placebo in the treatment of patients with active AS, and (2) the study provided endpoints for the clinical efficacy and safety of secukinumab or adalimumab. The exclusion criteria included (1) duplicate data, and (2) the study did not contain the necessary data for inclusion. The primary endpoint for efficacy was the number of patients who achieved the Assessment in Spondyloarthritis International Society (ASAS) response criteria of $\geq$20% (ASAS20) or $\geq$40% (ASAS40). ASAS20 is defined as an improvement of $\geq$20% and absolute improvement of $\geq$1 unit (on a 10-unit scale) in at least three of the four main ASAS domains at week 12 to 16, while the safety outcome was based on the number of patients who had experienced serious adverse effects [16]. The secondary endpoint for efficacy was the number of patients who achieved ASAS40. Two independent reviewers obtained the data from original studies. Any discrepancy between the reviewers was resolved by consensus. The data obtained from each publication included the first author, year of publication, country in which the study was performed, dose of secukinumab and adalimumab, time when outcomes were evaluated, and outcomes for efficacy and safety. We performed a network meta-analysis in accordance with the guidelines provided by the preferred reporting items for systematic reviews and meta-analyses statement [17].

Evaluation of statistical associations for network meta-analysis

For RCTs that compared multiple doses of secukinumab and adalimumab in different arms, the results were analyzed simultaneously. Direct data is an estimate of head-to-head comparison, for example, direct comparison of A versus B. In contrast, indirect data is an estimate of comparison of A versus B obtained through the common comparator C in the network, when there are direct comparisons of A versus C and B versus C. The efficacy and safety of secukinumab and adalimumab in different arms were ordered according to the probability of being ranked as the best performing regimen. We used a Bayesian random-effects model for network meta-analysis using NetMetaXL [18] and the WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). We used the Markov Chain Monte Carlo

method to estimate the pooled effect sizes [13]. All chains were run with 10,000 burn-in iterations followed by 10,000 monitoring iterations. Information on relative effects was converted to a probability that a treatment performed the best. The ranking of each treatment—called the surface under the cumulative ranking curve (SUCRA) [19], which is expressed as a percentage, was also assessed. SUCRA is 100% when a treatment is certain to be the best and 0% when it is certain to be the worst treatment. The league table presents summary estimates by ranking the treatments in order, beginning with the one with the highest impact on outcome as determined by SUCRA [19]. We reported the pairwise odds ratio (OR) and Bayesian credible interval (CrI) with a 95% confidence interval (CI). Trial results were adjusted for multiple treatment arms. Pooled results were considered statistically significant if the confidence interval did not contain the value 1.

Test for inconsistency

Inconsistency refers to the extent of disagreement between direct and indirect data [20]. Assessment of inconsistency is important for conducting a network meta-analysis [21]. We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to assess the network inconsistency between direct and indirect estimates in each loop [22]. A sensitivity test was performed by comparing the random and fixed effects models.

RESULTS

Meta-analysis studies

A total of 361 studies were identified through an electronic or manual search, and six were selected for a full-text review based on the title and abstract details. However, one of them was subsequently excluded as it had duplicate data. Therefore, five RCTs including 1,483 patients (715 efficacy-related events and 32 safety-related events) met the inclusion criteria [8-12] (Figure 1, Tables 1-3). All of the RCTs provided data related to both efficacy and safety, except for one that showed efficacy data only [11]. The evidence network diagram shows the data related to the number of studies that compared the different treatments and the number of patients included in each treatment group (Figure 2). There were 6 pairwise comparisons, including 4 direct comparisons and 4 treatments comprising placebo, secukinumab 75 mg, secukinumab 150 mg, and adalimumab 40 mg (Figure 2). Patients received intravenous loading infusions of secukinumab 10 mg/kg at weeks 0, 2 and 4, or subcutaneous injections

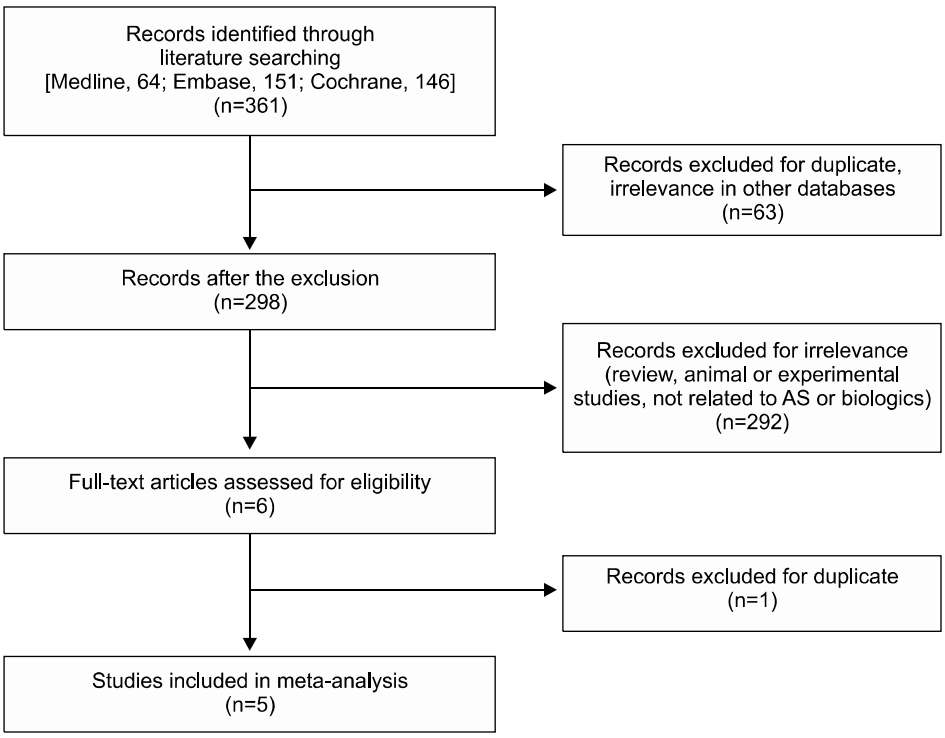

Figure 1. Flow diagram of the study selection process. AS: ankylosing spondylitis.

Table 1. Characteristics of individual studies included in the network meta-analysis

Study	Total	Drugs	Patient	ASAS20	Serious adverse event	Follow-up period for evaluation (wk)
Kivitz, 2016 [8]	150	Secukinumab 150 mg	74	43	0	16
		Placebo	76	28	1	
Baeten-1, 2015 [9]	371	Secukinumab 150 mg	125	76	3	16
		Secukinumab 75 mg	124	74	2	
		Placebo	122	35	4	
Baeten-2, 2015 [9]	219	Secukinumab 150 mg	72	44	4	16
		Secukinumab 75 mg	73	30	4	
		Placebo	74	20	3	
Huang, 2014 [10]	344	Adalimumab 40 mg	229	154	2	12
		Placebo	115	37	0	
Lambert, 2007 [11]	82	Adalimumab 40 mg	38	18	NA	12
		Placebo	44	12	NA	
van der Heijde, 2006 [12]	315	Adalimumab 40 mg	208	121	6	12
		Placebo	107	22	3	

Values are presented as number. ASAS20: Assessment of Spondyloarthritis International Society 20 response criteria (improvement of ≥20% and absolute improvement of ≥1 unit [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain) [16], NA: not available.

Table 2. Characteristics of individual studies included in the network meta-analysis

Study	Drugs	Age (yr)	Disease duration (yr)	Male	HLA-B27	BASDAI
Kivitz, 2016 [8]	Secukinumab 150 mg	42.1～42.9*	5.2～6.0*	NA	NA	NA
	Placebo	42.1～42.9*	5.2～6.0*	NA	NA	NA
Baeten-1, 2015 [9]	Secukinumab 150 mg	40.1±11.6	6.5±6.9	67	69	6.4±1.6
	Secukinumab 75 mg	42.3±13.2	7.9±9.7	71	80	6.1±1.4
	Placebo	43.1±12.4	8.3±8.9	70	74	6.5±1.5
Baeten-2, 2015 [9]	Secukinumab 150 mg	41.9±12.5	7.0±8.2	64	79	6.6±1.5
	Secukinumab 75 mg	44.4±13.1	5.3±7.4	70	73	6.1±1.3
	Placebo	43.6±13.2	6.4±8.9	76	78	6.8±1.3
Huang, 2014 [10]	Adalimumab 40 mg	30.1±8.7	3.0±3.8	80.8	95.6	6.0±1.4
	Placebo	29.6±7.5	3.0±3.2	82.6	94.8	6.2±1.4
Lambert, 2007 [11]	Adalimumab 40 mg	41.9±11.1	14.5±9.0	76.3	86.8	6.2±1.7
	Placebo	40.0±10.9	12.1±8.7	81.8	81.8	6.5±1.6
van der Heijde, 2006 [12]	Adalimumab 40 mg	41.7±11.9	11.3±9.99	75.5	78.4	6.3±1.7
	Placebo	43.4±11.3	10.8±8.34	73.8	79.4	6.3±1.7

Values are presented as range, mean±standard deviation, number only, or percentage. HLA: human leukocyte antigen, BASDAI: bath ankylosing spondylitis disease activity index, NA: not available. *Mean.

Table 3. Characteristics of individual studies included in the network meta-analysis

Comparison	Study	Patient
Placebo	6	538
Secukinumab 150 mg	3	271
Secukinumab 75 mg	2	199
Adalimumab 40 mg	3	475

Values are presented as number.

of secukinumab 75, or 150 mg at weeks 0, 1, 2, and 3. This was followed by subcutaneous secukinumab 75, or 150 mg every 4 weeks. Adalimumab (40 mg) was injected subcutaneously every other week. The relevant features of the studies included in the meta-analysis are provided in Tables 1-3.

Network meta-analysis on the efficacy of secukinumab and adalimumab in the RCTs

Adalimumab 40 mg is listed in the top left of the diagonal of the league table (Table 4) because it was associated with the most favorable SUCRA for the ASAS20 response rate, while placebo is listed in the bottom right of the diagonal of the league table because it was associated with the least favorable results. For interpretation purposes, the results are read from top to bottom and left to right.

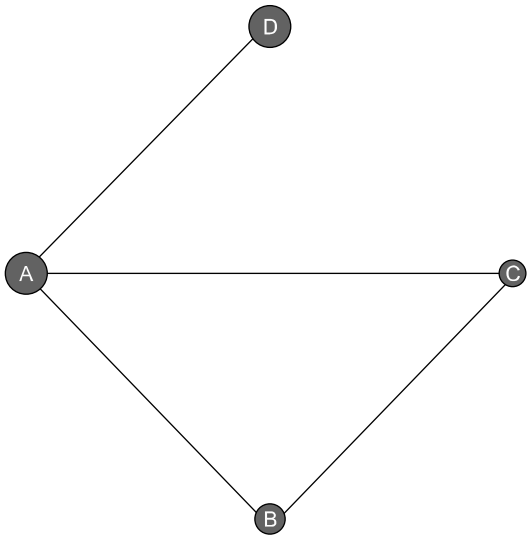

Figure 2. Evidence network diagram of comparisons for network meta-analysis. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). (A) Placebo. (B) Secukinumab 150 mg. (C) Secukinumab 75 mg. (D) Adalimumab 40 mg.

The ASAS20 response rate was significantly higher in the adalimumab group than that in the placebo group (OR, 4.26; 95% CrI, 2.09～8.08) (Table 4, Figure 3). Similarly, the ASAS20 response rate was significantly higher with secukinumab 150 mg, and 75 mg (OR 3.35, 95% CrI 1.73～6.56; OR 2.44, 95% CrI 1.06～5.05) (Table 4, Figure 3). Both secukinumab and adalimumab achieved a significant ASAS20 response compared to placebo (Table 4). Adalimumab 40 mg showed a numerically higher efficacy than secukinumab did. However, no statistically significant difference was found between adalimumab 40 mg and secukinumab 75 mg, and 150 mg for the ASAS20 response rate. The ASAS40 response rate showed a similar distribution pattern to the ASAS20 response rate (Table 4). The SUCRA is 1 when a treatment is certain to be the best, and 0 when a treatment is certain to be the worst. SUCRA values enable the ranking of treatments for a particular outcome. SUCRA simplifies the information about the effect of each treatment into a single number. Thus, it may help to guide decision-making. The ranking probability based on SUCRA (Table 5) indicated that adalimumab at a dose of 40 mg had the highest probability of being the best treatment for achieving the ASAS20 response rate (SUCRA=0.8753), followed by secukinumab 150 mg (SUCRA=0.7051), secukinumab 75 mg (SUCRA=0.4113), and placebo (SUCRA=0.0083). The ASAS40 response rate showed a similar distribution pattern to the ASAS20 response rate (Table 5).

Table 4. Network meta-analyses comprising the effects for all contrasts along with ORs and 95% credible intervals

A. ASAS20. OR＞1 means the treatment in top left is better			
Adalimumab 40 mg			
1.27 (0.47～3.19)	Secukinumab 150 mg		
1.74 (0.63～4.95)	1.38 (0.67～3.13)	Secukinumab 75 mg	
4.26 (2.09～8.08)	3.35 (1.73～6.56)	2.44 (1.06～5.05)	Placebo
B. ASAS40			
Adalimumab 40 mg			
1.72 (0.78～4.18)	Secukinumab 150 mg		
2.47 (1.04～6.20)	1.42 (0.77～2.63)	Secukinumab 75 mg	
6.79 (3.80～13.10)	3.93 (2.19～6.90)	2.76 (1.41～5.29)	Placebo
C. Safety. OR＜1 means that the treatment in the top left block is better			
Secukinumab 75 mg			
0.91 (0.16～5.58)	Secukinumab 150 mg		
0.74 (0.11～3.85)	0.80 (0.13～3.55)	Placebo	
0.41 (0.02～4.60)	0.45 (0.02～4.64)	0.56 (0.05～3.44)	Adalimumab 40 mg

ASAS: Assessment in Spondyloarthritis International Society, OR: odds ratio.

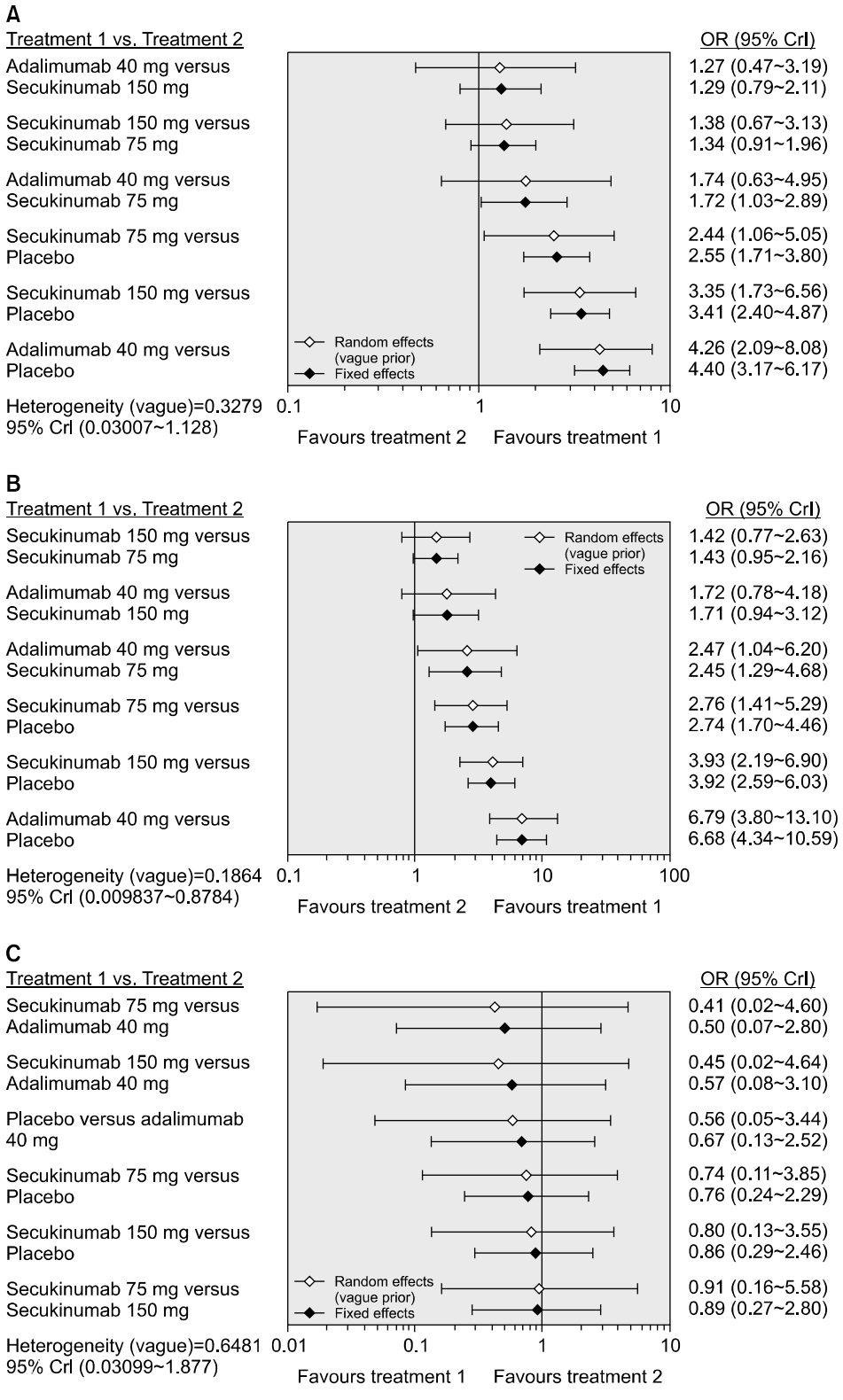

Figure 3. Results of the Bayesian network meta-analysis of randomized controlled studies on the relative efficacy (A: ASAS20, B: ASAS40) and safety (C) of secukinumab and adalimumab. ASAS: Assessment in Spondyloarthritis International Society, OR: odds ratio, CrI: credible interval.

Network meta-analysis on the safety of secukinumab and adalimumab in RCTs

We considered the number of serious adverse events as the safety outcome. The number of serious adverse events was lower, albeit not statistically significant, in secukinumab at doses of 75 mg and 150 mg than in adalimumab at 40 mg dose (OR 0.41, 95% CrI 0.02～4.60; OR 0.45, 95% CrI 0.02～4.54) (Table 4, Figure 3). The num-

ber of serious adverse events did not differ significantly between the five treatment options (Table 4, Figure 3).

Inconsistency and sensitivity analysis

Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility for inconsistencies that might significantly affect network meta-analysis results (Figure 4). This was confirmed via random and fixed effects, suggesting that the results of this network meta-analysis were robust (Figure 3).

Table 5. Rank probability in terms of efficacy based on the number of patients that achieved an ASAS20 or ASAS40 response, and the safety based on the number of serious adverse events

Treatment	SUCRA
Efficacy: ASAS20	
Adalimumab 40 mg	0.8753
Secukinumab 150 mg	0.7051
Secukinumab 75 mg	0.4113
Placebo	0.0083
Efficacy: ASAS40	
Adalimumab 40 mg	0.9675
Secukinumab 150 mg	0.6571
Secukinumab 75 mg	0.3732
Placebo	0.0022
Safety	
Secukinumab 75 mg	0.6560
Secukinumab 150 mg	0.6064
Placebo	0.4826
Adalimumab 40 mg	0.2550

ASAS: Assessment in Spondyloarthritis International Society, SUCRA: surface under the cumulative ranking curve.

DISCUSSION

We performed a network meta-analysis to compare the relative efficacy and safety of secukinumab and adalimumab to a placebo in patients with active AS. This analysis approach was chosen because it enables an indirect comparison of multiple treatments, which are either lacking or have insufficient direct comparisons. Our network meta-analysis assessed the number of patients who achieved an ASAS20 and ASAS40 response and the number of serious adverse effects. Our network meta-analysis shows that the ASAS20 response rate was significantly higher with adalimumab at a dose of 40 mg and with secukinumab dosages of 75 mg, and 150 mg. Adalimumab at a dose of 40 mg showed a numerically higher efficacy than secukinumab. However, no statistically significant difference was found for the ASAS response rate between adalimumab at 40 mg and secukinumab at 75 mg, and 150 mg. The ASAS40 response rate showed a similar distribution pattern to the ASAS20 response rate. With respect to safety, no significant difference was observed in the number of serious adverse events among the four treatment groups, suggesting a comparable safety among the secukinumab 75 mg, and 150 mg, adalimumab 40 mg, and the placebo group. In summary, secukinumab and adalimumab were effective in the treatment of patients with active AS and showed an acceptable safety profile.

IL-17A plays an important role in the pathogenesis of AS [6]. Our analysis suggest that all three doses of subcutaneous secukinumab are effective in AS, suggesting that secukinumab is a good alternative to anti-TNF agent. Use of TNF inhibitors has improved the management of AS,

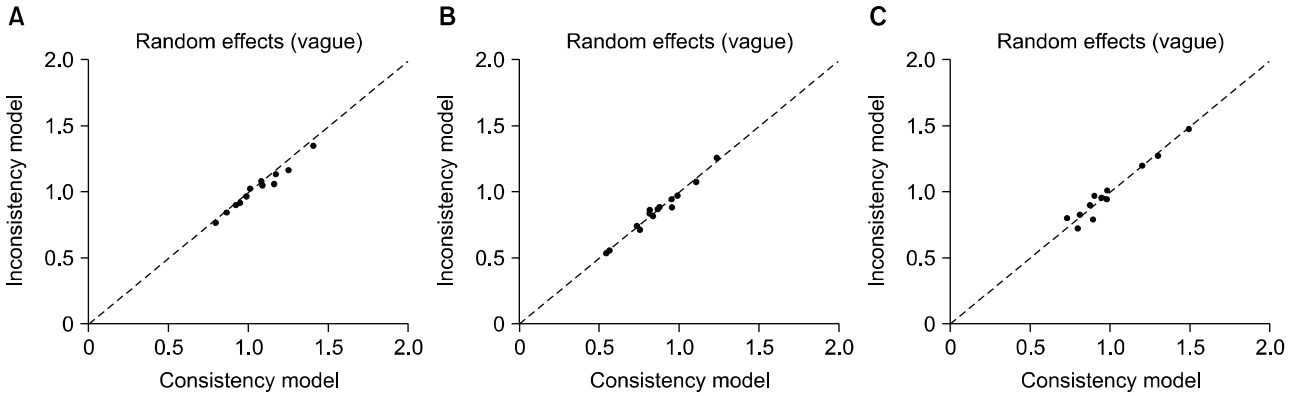

Figure 4. Inconsistency plot for the efficacy (A: ASAS20, B: ASAS40) and safety (C) of secukinumab and adalimumab. Plot of the individual data points' posterior mean deviance contributions for the consistency model (horizontal axis) and the unrelated mean effects model (vertical axis) along with the line of equality. ASAS: Assessment in Spondyloarthritis International Society.

but a substantial proportion of patients show inadequate responses to such therapies. An unmet need exists for AS therapies due to drug intolerance, non-responsiveness, and therapeutic resistance. Thus, the need exists for additional treatment options with novel mechanisms of action. Apremilast is a novel, oral phosphodiesterase 4 inhibitor that regulates inflammatory mediators [23]. Apremilast, abatacept, IL-6 blockade, rituximab, and tofacitinib have shown no or mixed results for the treatment of AS [24]. Secukinumab is the first anti-IL-17A monoclonal antibody to provide evidence for efficacy of a non-TNF targeted therapy in AS. IL-17A and its receptor are expressed in synovial tissues and may mediate the biological functions responsible for joint and entheseal inflammation. This could lead to damage and tissue remodeling. Ustekinumab is a human Immunoglobulin G 1 κ monoclonal antibody that binds to the common p40 subunit shared by interleukins 12 and 23, which inhibits their binding to the interleukin 12R β 1 receptor on the surface of T cells, natural killer cells, and antigen-presenting cells, which prevents the subsequent receptor signaling and activation [25]. Interleukins 12 and 23 have an important role in psoriatic arthritis and interleukin 23 triggers IL-17A production [26]. Ustekinumab, is currently in clinical trials for AS [27]. It also validates the inhibition of IL-17A as a potential therapeutic approach. IL-17 blocking agents are currently being explored as a therapeutic strategy for autoimmune and inflammatory diseases.

There have been two recently published network meta-analyses [14,15]. Our network meta-analysis differs from previous network meta-analyses on biologic agents in patients with active AS [14,15], because in the present study the latest studies were included, and relative safety of secukinumab and adalimumab was additionally conducted. However, the result of this network meta-analysis regarding the relative efficacy of secukinumab 75 mg, 150 mg and adalimumab 40 mg in patients with active AS is in agreement with previous studies.

Our results should be interpreted with caution because of the following shortcomings of the present study. First, the follow-up time points were relatively short treatment periods (12 and 16 weeks). Therefore, the follow-up duration was too short for an evaluation of the long-term effects of the treatments. Future longer comparative studies are warranted. Second, the design and patient characteristics of the trials analyzed were heterogeneous; these inter-study differences may have affected the results of our network meta-analysis. Third, our study did not comprehensively address the efficacy and safety outcomes of secukinumab and adalimumab in AS. We had only focused on the treatment efficacy based on the number of patients who achieved an ASAS20 or ASAS40 response and on safety according to the number of serious adverse effects, without assessing various outcomes. Specifically, the number of serious adverse events may not be sufficient as a safety outcome measure because of its low frequency.

CONCLUSION

By using a Bayesian network meta-analysis involving five RCTs comparing five different treatment groups, we found that secukinumab at 75 mg and 150 mg and adalimumab at 40 mg were effective for treatment of patients with active AS. Additionally, the therapies were not associated with a significant risk for serious adverse events. Nevertheless, long-term studies are needed to determine the relative efficacy and safety of secukinumab in a large number of patients with active AS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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