Model-Based Meta-Analysis in Ankylosing Spondylitis: A Quantitative Comparison of Biologics and Small Targeted Molecules

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Information on the comparative efficacy is important for drug development as well as drug therapy. Up to now, the relative efficacy of approved biologics and many agents under investigation in ankylosing spondylitis (AS) are still unclear. The objective of this study was to quantify the relative efficacy and time course of various treatments measured by the Ankylosing Spondylitis Assessment Study group response criteria 20 scores (ASAS20), change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI). There were 34 double-blinded trials of 10 biologics and small molecules encompassing 5,339 patients with AS were included in this analysis. Three mathematical models with nonparametric placebo estimations were used to describe the longitudinal profile for the above three efficacy measures. The results detected significant differences among included treatments, and infliximab and golimumab were found to have the highest efficacy in given dosage regimens across all measures.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Five tumor necrosis factor inhibitors and one biologic acting on interleukin-17 have been proved for the treatment of AS. A number of other biologics and small molecules are currently in clinical trials. However, quantitative comparison based on their longitudinal profile remains unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Three longitudinal models for the three end points (Ankylosing Spondylitis Assessment Study group response criteria 20 scores (ASAS20), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI)) commonly reported in clinical trials of AS are presented. The onset and magnitude of response for each drug in each end point are compared.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This analysis provided rank orders of efficacy for the existing treatments and those under investigation. It also suggested that ASAS20 demonstrated immediate attainment of maximal effect for the majority of drugs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This analysis could provide a quantitative understanding for the selection of approved treatments in AS. In addition, the framework presented may be used for the development of biological therapies on the horizon.

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease primarily characterized by the inflammation of the axial skeleton. Other manifestations include peripheral arthritis, enthesitis, and anterior uveitis.[1] It mainly affects the patients in the third decade of life with a prevalence rate between 0.1% and 1.4% globally.[2] The pharmaceutical therapy of AS involves nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (DMARDs), and biologics. NSAIDs are the first-line drugs for AS, but there are still some patients who do not respond to them. DMARDs may be used in case of peripheral arthritis, but they show no evidence for the axial manifestations.[3] For those who failed or could not tolerate NSAIDs, the use of biologics is strongly recommended.[4] Until now, six biologics, including five antitumor necrosis factor (TNF) inhibitors and one interleukin (IL)-17 inhibitor, have been proved for the treatment of AS, and a number of other biologics are under investigation. However, no particular agent is preferred in the guideline[3] due to the deficiency of head-to-head comparison.

Several meta-analyses have been conducted to discover the potential difference among the available treatments for AS.[5–9] However,

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no statistical difference among these treatments was observed, and their relative clinical efficacy remains unknown. The common drawback of previous meta-analyses were that primarily focusing on the single-end point data, they failed to take into account the varied time points of outcomes that many randomized controlled trials reported, thus leading to the inadequate utilization of the data.

Longitudinal model-based meta-analysis is an extension of traditional meta-analysis.[10] By encompassing longitudinal data from the literature, it allows the evaluation of the effect and duration of drug action and could provide accurate assessment of the true response and, consequently, a more valid comparison between treatments.[11] Therefore, it could offer a more informative view of the data than the traditional meta-analyses. The objective of our longitudinal meta-analysis was to assess the relative efficacy and onset across different systemic agents, including those approved and those undergoing investigation. Efficacy was measured by three end points commonly reported in the clinical trials of AS: Ankylosing Spondylitis Assessment Study group response criteria 20 (ASAS20),[12] change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[13] and Bath Ankylosing Spondylitis Functional Index (BASFI).[14]

RESULTS

Available data

A total of 34 trials, encompassing 80 treatment arms and 5,339 patients, were included in the analysis. In total, all trials recruited patients with active AS. Almost all trials except for one[15] have documented a background treatment of NSAIDs. Eighty percent of trials allowed a background treatment of DMARDs. Nearly all trials were placebo controlled, with one exception that was active controlled.[16]

An overview of the included studies is displayed in **Table 1**. Full references and additional information of included studies and the flow chart of the detailed process of study selection are presented in the **Supplementary Materials S1**.

The final database involved eight biological agents and two small targeted molecules, including TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), IL-17 inhibitors (secukinumab), IL-6 inhibitors (sarilumab and tocilizumab), Janus kinase inhibitors (tofacitinib), and phosphodiesterase 4 inhibitors (apremilast). A summary of all available end points indicated that ASAS20, BASDAI, and BASFI were the most reported outcomes. ASAS20 values were reported in 33 trials, and BASDAI and BASFI were available for 29 and 28 trials, respectively. All the BASDAI or BASFI values were translated to ΔBASDAI (change from baseline in BASDAI) and ΔBASFI (change from baseline in BASFI). The dataset used in our analysis can be found in **Data S1**.

ASAS20 model

The drug effect measured by ASAS20 was described by the following equations:

For i.v. golimumab,

$$Edrug_{\mathrm{ASAS20}} = E_{\mathrm{max}_{\mathrm{gol,iv}}} \cdot \left(1 - e^{-k_{\mathrm{gol,iv}} \cdot \mathrm{time}}\right) \quad (1)$$

For other drugs,

$$Edrug_{\mathrm{ASAS20}} = f\left(E_{\mathrm{max}_{\mathrm{drug}}}, \mathrm{dose}, \mathrm{regimen}\right) \quad (2)$$

For i.v. golimumab (Eq. 1), E_{drug} is an exponential function dependent on time where $E_{\mathrm{max}_{\mathrm{gol,iv}}}$ represents the maximum efficacy, and $k_{\mathrm{gol,iv}}$ represents the rate constant describing the onset of i.v. golimumab. For other drugs (Eq. 2), E_{drug} is a function without time and is dependent on dose, regimen, and $E_{\mathrm{max}_{\mathrm{drug}}}$, which was individually estimated for each drug. In a word, except for the i.v. golimumab regimen for which we estimated a time-varying drug effect, other drugs exhibited an immediate attainment of the maximum treatment effect (**Figure 1**). The final parameter estimates are listed in **Table 2**. The time to reach 50% of the maximum effect (ET_{50}) of i.v. golimumab was estimated to be about 2.7 weeks, and the time to reach 90% of the maximum effect (ET_{90}) was nearly 9.0 weeks.

The dose-response relationship was tested. No significant impact of regimen or dose on maximum effect (E_{max}) was found for etanercept, and no impact of dose was found on s.c. golimumab. In contrast, two regimens of certolizumab pegol were shown to have slightly different efficacy. In addition, the impact of regimen and dose was found in secukinumab, and the general effect of s.c. secukinumab regimen of 75 mg 0, 1, 2, 3, 4, and once every 4 weeks (q4w) was noticeably lower than other secukinumab regimens and sarilumab regimen of 150 mg q.w. was shown to be the most effective regimen. The general effect of tofacitinib of 5 mg b.i.d. was found to be higher than the other dosage of tofacitinib (2, 10 mg b.i.d.). For infliximab, a linear dose-response relationship was defined with 5 mg/kg 0, 2, 6, and once every 6 weeks (q6w) providing the highest efficacy (**Table 2**).

Six covariates (percentage of male, disease duration, age, BASDAI, BASFI, and C-reactive protein (CRP)) were tested and only baseline BASFI value was included in the final model. The estimated covariate parameter value of −0.69 (−1.25, −0.14) means that the lower the baseline BASFI values, the higher the ASAS20 response.

The model simulation of the median ASAS20 values (with simulated placebo effect) along with their 95% intervals for included treatments at week 12, assuming a typical BASFI value of 5.4, is shown in **Figure 2a**. To generate the simulation, we developed a longitudinal placebo model using available data, with a result of the placebo effect of 26.3% at week 12 (dashed line in **Figure 2a**). Among all treatments, TNF inhibitors were the most efficacious treatment with i.v. golimumab showing the best response (76.97%; confidence interval (CI) = 61.58 to 87.34%) at week 12, followed by infliximab 5 mg/kg 0, 2, 6, and q6w (74.48%; CI=67.94 to 79.89%). Other classes of biologics were less effective than anti-TNFα. Sarilumab and tocilizumab did not show significant efficacy compared with placebo with model-estimated 95% CIs crossing the dashed line representing the placebo effect. Among small molecules, a significant efficacy was only found in tofacitinib.

ΔBASDAI model

The time-varying drug effect in ΔBASDAI was described by an exponential model as follows:

$$Edrug_{\Delta\mathrm{BASDAI}} = E_{\mathrm{max}_{\mathrm{drug}}} \cdot \left(1 - e^{-k_{\mathrm{AR}} \cdot \mathrm{time}}\right) \quad (3)$$

Where E_{max} was set individually for each treatment and AR represents different administration routes. The final estimated

Table 1 Summary of available information for each drug in the analysis

Drug	Trials	Patients	Route (regimen)	Treatment duration (weeks)	Percentage of male (%)[a]	Disease duration (years)[a]	Baseline BASDAI[a]	Baseline BASFI[a]	Total Arms	Arms with ASAS20	Arms with BASDAI	Arms with BASFI
TNF-α inhibitor												
Adalimumab	3	475	s.c. (40 mg q2w)	12–24	76.30 (75.50, 80.80)	11.30 (3.00, 14.50)	6.20 (6.00, 6.30)	5.20 (4.30, 5.30)	3	3	3	3
Certolizumab pegol	1	121	s.c. (200 mg q2w) s.c. (400 mg q4w)	24	72.75 (72.30, 73.20)	NA	6.35 (6.20, 6.50)	5.65 (5.60, 5.70)	2	2	2	2
Etanercept	12	1072	s.c. (25 mg, 50 mg biw) s.c. (50 mg q.w.)	6–24	77.81 (65.00, 95.00)	10.10 (7.03, 19.00)	6.08 (5.41, 6.50)	5.66 (3.38, 6.30)	14	13	12	11
Golimumab	5	524	s.c. (50, 100 mg q4w) i.v. (2 mg/kg 0, 4, q8w)	16–24	82.60 (70.00, 92.30)	5.18 (4.05, 8.00)	6.80 (6.15, 7.10)	5.20 (4.61, 6.30)	6	6	3	6
Infliximab	5	321	i.v. (3, 5 mg/kg 0, 2, 6, q6w) i.v. (5 mg/kg 0, 2, 6, q8w)	12–30	78.10 (68.00, 82.14)	11.70 (7.70, 16.40)	6.55 (6.45, 6.60)	6.20 (5.40, 6.90)	5	5	5	4
IL-17 inhibitor												
Secukinumab	4	568	s.c. (75, 150 mg 0, 1, 2, 3, 4, q4w) i.v. (10 mg/kg q3w) i.v.-s.c. (10 mg/kg 0, 2, 4w followed by 75, 150, 300 mg q4w)	6–16	65.80 (58.00, 71.00)	6.50 (5.30, 10.10)	6.60 (6.10, 7.10)	5.60 (5.40, 6.40)	7	7	7	2
IL-6 inhibitor												
Sarilumab	1	251	s.c. (100, 150 mg q.w.) s.c. (100, 150, 200 mg q2w)	12	71.20 (61.20, 80.00)	7.13 (5.55, 8.55)	NA	4.05 (3.95, 4.25)	5	5	5	5
Tocilizumab	1	51	i.v. (8 mg/kg q4w)	12	71.00 (71.00, 71.00)	5.40 (5.40, 5.40)	6.62 (6.62, 6.62)	6.24 (6.24, 6.24)	1	1	1	1

(Continues)

Table 1 (Continued)

Drug	Trials	Patients	Route (regimen)	Treatment duration (weeks)	Percentage of male (%)[a]	Disease duration (years)[a]	Baseline BASDAI[a]	Baseline BASFI[a]	Total Arms	Arms with ASAS20	Arms with BASDAI	Arms with BASFI
JAK inhibitor												
Tofacitinib	1	156	p.o. (2, 5, 10 mg b.i.d.)	12	73.10 (65.40, 75.00)	3.50 (1.50, 4.10)	6.90 (6.50, 7.00)	5.70 (5.50, 5.80)	3	3	3	3
PDE4 inhibitor												
Apremilast	1	17	p.o. (30 mg b.i.d.)	12	NA	20.88 (20.88, 20.88)	4.79 (4.79, 4.79)	4.55 (4.55, 4.55)	1	1	1	1
Placebo	33	1783		6–30	78.00 (52.60, 100.00)	10.00 (3.00, 23.00)	6.40 (4.36, 7.62)	5.60 (3.20, 6.10)	33	32	27	25
Total	34	5339		6–30	76.00 (52.60, 100.00)	8.37 (1.50, 23.0)	6.47 (4.36, 7.62)	5.60 (3.20, 6.90)	80	78	69	63

ASAS20, ≥ 20% improvement in the Assessment of SpondyloArthritis International Society criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; IL, interleukin; JAK, Janus kinase; NA, not available; PDE, phosphodiesterase; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks; q6w, once every 6 weeks; q8w, once every 8 weeks; TNF, tumor necrosis factor.

[a]Data are shown as median (range).

parameters are listed in **Table 3**. Intention to estimate separate k for each drug did not improve the model fit. Instead, we identified different rate constants of onset for different administration routes. With four available routes (s.c., p.o., i.v., and s.c. after i.v. loading regimen (i.v.-s.c.)[17,18]), we combined the onset of i.v. and i.v.-s.c. as $k_{\cdot i.v.}$, and s.c. and p.o. as $k_{\cdot s.c.}$, because the data for p.o. regimen are too limited for separate analysis.

In contrast to the ASAS20 model, a regimen difference in the effect of etanercept was detected. Moreover, the response of tofacitinib 5 mg did not vary much from the other dosage of tofacitinib. The onset for drugs by i.v. administration routes (ET_{50} = 0.8 week, ET_{90} = 2.8 weeks) was significantly faster than drugs by s.c. routes (ET_{50} = 2.1 weeks, ET_{90} = 7.0 weeks; **Table 3**).

Among all the covariates investigated, only the percentage of male patients was included as covariate. The estimated covariate parameter value of −0.72 (−1.50, 0.05) indicates that female patients are more likely to show greater improvement in BASDAI than male patients.

The parameters of the BASDAI model were used to simulate placebo-adjusted change from baseline in BASDAI scores at week 12, assuming a typical trial with 75% male patients (**Figure 2b**). Similar to the result of the ASAS20 model, TNF inhibitors were still the most effective treatment. Infliximab 5 mg/kg 0, 2, 6, and q6w resulted in the greatest placebo-corrected change (−2.46; CI = −2.80 to −2.11) in BASDAI at week 12, followed by s.c. golimumab (−2.11; CI = −2.41 to −1.82) (as the trial investigating i.v. golimumab did not report BASDAI scores). IL-6 inhibitors (sarilumab and tocilizumab) did not significantly improve the BASDAI scores with 95% CI crossing null.

ΔBASFI model

The formula of drug effect in ΔBASFI was described as below:

For certolizumab pegol,

$$Edrug_{\Delta\text{BASFI}} = E_{\max_{\text{drug}}} \tag{4}$$

For other drugs,

$$Edrug_{\Delta\text{BASFI}} = E_{\max_{\text{drug}}} \cdot \left(1 - e^{-k_{\text{general}} \cdot \text{time}}\right) \tag{5}$$

The final parameters are listed in **Table 3**. The onset of all drugs (k_{general}) was set to the same value except certolizumab pegol as it exhibited an immediate attainment of maximum effect. The majority of drugs, except certolizumab pegol, achieved ET_{50} at 2.3 weeks and ET_{90} at 7.7 weeks.

The inclusion of dosage regimen impact of etanercept did not significantly improve the model. The effect of i.v. golimumab was not able to be estimated separately as only one point was available for the ΔBASFI model. However, the introduction of a separate E_{max} parameter for s.c. golimumab regimen of 50 mg q4w improved the model significantly, indicating that the regimen had a lower effect in the improvement of BASFI than the s.c. golimumab regimen of 100 mg q4w and i.v. golimumab.

The percentage of male patients was also included as covariate. The estimated covariate parameter value of −1.60 (−2.54, −0.66) means that female patients are more likely to show greater improvement in BASFI than male patients.

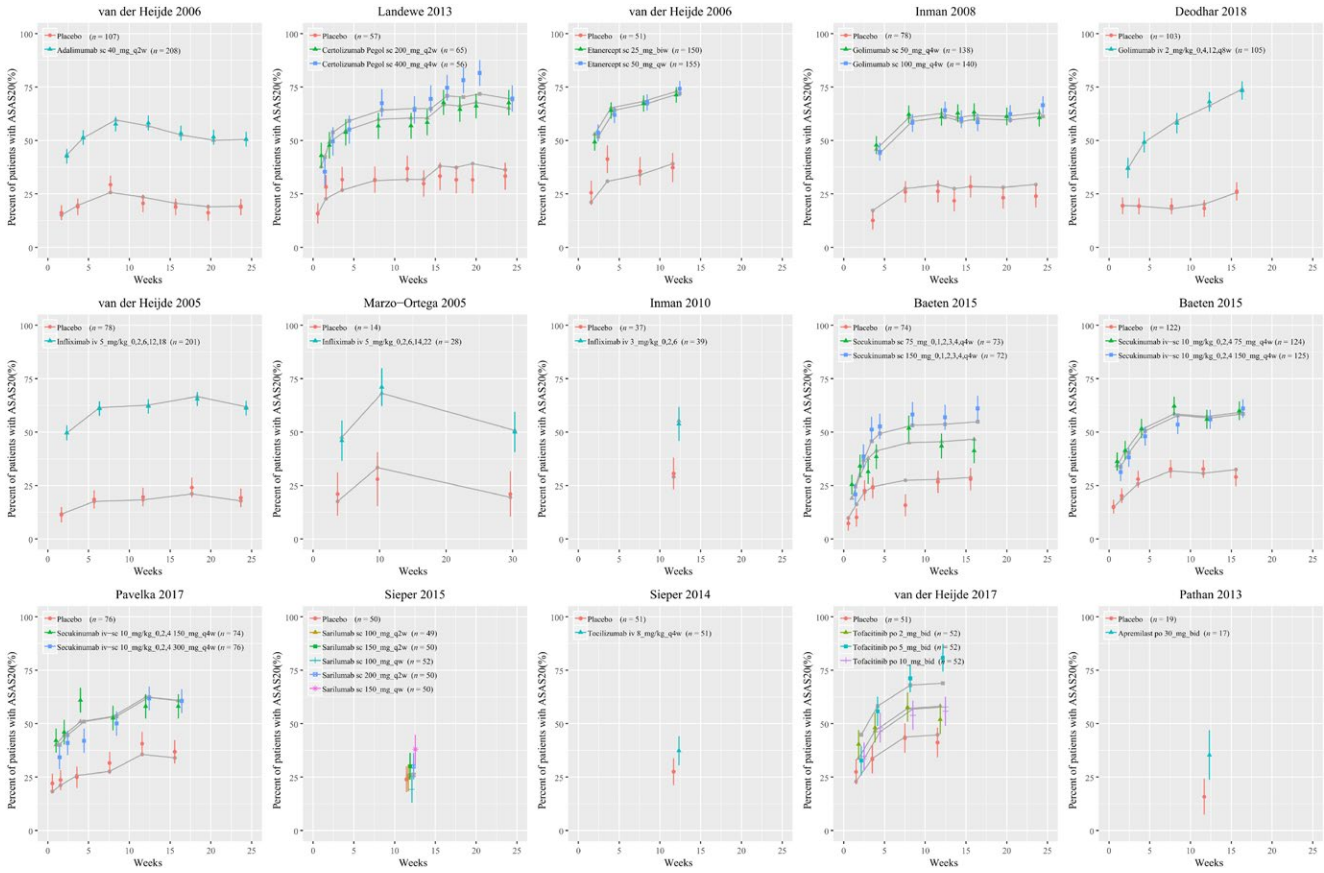

Figure 1 Model fitted time-course plots of response rate for ASAS20 for representative trials. Color symbols and vertical bars are observed mean and standard error of time points; gray symbols and lines are the fitted values. ASAS20, ≥ 20% improvement in the Assessment of SpondyloArthritis International Society criteria; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks; q8w, once every 8 weeks. [Colour figure can be viewed at wileyonlinelibrary.com]

The simulation of placebo-corrected ΔBASFI, assuming a typical trial with 75% male patients is shown in **Figure 2c**. It reveals that golimumab, regardless of administration routes, had the best response in BASFI changes among all the treatments (−1.90; CI = −2.11 to −1.68), followed by infliximab 5 mg/kg 0, 2, 6, and q6w (−1.82; CI = −2.16 to −1.50). Apremilast was able to significantly improve the BASFI scores (−1.46; CI = −2.25 to −0.64) with a large 95% CI.

Residual correlation

After comparing the model fit, an autoregressive process of order 1 (AR1) was used to account for residual correlation for the ASAS20 model, the ΔBASDAI model, and the ΔBASFI model.

Model evaluation

The diagnostic plots for the three models did not show obvious misspecification (**Figure S1**). The model-fitted time-course plots of representative trials for three models are shown in **Figures 1, 3, and 4**, respectively. The model-fitted time-course plots for additional trials can be found in **Figure S2**.

DISCUSSION

Our meta-analysis provided a quantitative method for the efficacy comparison across 10 drugs. Three different end points were evaluated in this analysis. One is binary end point (ASAS20) and two are continuous end points (ΔBASDAI and ΔBASFI) each assessing the response to treatment (function, pain, global assessment, and inflammation), improvement in disease activity (fatigue, pain, and stiffness) and physical function (the ability to perform and cope with activities of daily living). The characterization of all the three end points allowed the evaluation of three areas of drug impact and, thus, provided a comprehensive understanding of the drug efficacy. The physicians and patients could choose their favorable treatments depending on their priorities.

Generally, the efficacy trend is similar across the three measures: anti-TNF treatments were the most effective treatment as infliximab (5 mg/kg 0, 2, 6, and q6w) and i.v. golimumab provided the highest response. The lowest efficacy was observed in IL-6 inhibitors. These results are supported by a head-to-head open label study,[19] comparing the efficacy of infliximab and etanercept, and two previous meta-analyses,[5,7] in which the higher efficacy of infliximab was detected. However, there were still some small differences in the rank order across the three end points: apremilast ranked higher in the BASFI than in BASDAI and ASAS20, whereas certolizumab pegol ranked lower in BASFI.

Our longitudinal model-based meta-analysis enabled the estimation of drug onset. Generally, efficacy measured by ASAS20

Table 2 Final parameter estimates of ASAS20 model

Drugs	Route (regimen)	Estimate	95% CI
E_{max}			
Adalimumab	s.c. (40 mg q2w)	1.41	(1.19, 1.62)
Certolizumab pegol	s.c. (200 mg q2w)	1.21	(0.83, 1.59)
	s.c. (400 mg q4w)	1.42	(1.02, 1.82)
Etanercept	s.c. (25, 50 mg biw) s.c. (50 mg q.w.)	1.49	(1.32, 1.67)
Golimumab	s.c. (50, 100 mg q4w)	1.32	(1.11, 1.54)
	i.v. (2 mg/kg 0, 4, q8w)	2.37	(1.69, 3.05)
Infliximab (intercept)[a]	i.v. (5 mg/kg 0, 2, 6, q6w)	2.08	(1.77, 2.39)
Infliximab (slope)[a]	NA	−0.49	(−0.90, −0.07)
Secukinumab	s.c. (150 mg 0, 1, 2, 3, 4, q4w) i.v. (10 mg/kg q3w) i.v.-s.c. (10 mg/kg 0, 2, 4w followed by 75, 150, 300 mg q4w)	1.10	(0.92, 1.28)
Secukinumab	s.c. (75 mg 0, 1, 2, 3, 4, q4w)	0.77	(0.43, 1.11)
Sarilumab	s.c. (100 mg q.w.) s.c. (100, 150, 200 mg q2w)	0.10	(−0.47, 0.67)
Sarilumab	s.c. (150 mg q.w.)	0.54	(−0.12, 1.21)
Tocilizumab	i.v. (8 mg/kg q4w)	0.49	(−0.38, 1.37)
Tofacitinib	p.o. (2, 10 mg b.i.d.)	0.54	(0.10, 0.99)
Tofacitinib	p.o. (5 mg b.i.d.)	1.05	(0.53, 1.58)
Apremilast	p.o. (30 mg b.i.d.)	0.94	(−0.40, 2.28)
K			
Rate constant for the onset of i.v. golimumab	i.v. (2 mg/kg 0, 4, q8w)	0.26	(0.11, 0.63)
Covariate			
Baseline BASFI	NA	−0.69	(−1.25, −0.14)

ASAS20, ≥ 20% improvement in the Assessment of SpondyloArthritis International Society criteria; BASFI, Bath Ankylosing Spondylitis Functional Index; b.i.w, twice weekly; CI, confidence interval; E_{max}, maximum drug effect; *k*, rate constant for the onset of drug effect; NA, not available; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks; q6w, once every 6 weeks; q8w, once every 8 weeks.

[a]The dose-response relationship of infliximab is linear with a slope and an intercept, which is the maximum effect of infliximab 5 mg/kg 0, 2, 6, and q6w (i.e., the E_{max} of any dose of infliximab = infliximab (intercept) + infliximab (slope) * (5-dose)).

was shown to have the fastest onset, followed by ΔBASDAI and ΔBASFI. This may suggest that ASAS20, as a binary outcome, does not provide continuous measures of change as does ΔBASDAI and ΔBASFI.[20] It may also be that ASAS20 is less stringent and, therefore, it is easy to achieve in a short time. Overall, the immediate attainment of maximal ASAS20 response rate for most drugs indicates that the decision making in the development of AS treatments could be based on a shorter sampling duration of the ASAS20 response rate.

Dose and regimen information was also accounted for in this meta-analysis. The results suggest that, for etanercept and golimumab, higher dose (50 mg b.i.w for etanercept and 100 mg q4w for golimumab) does not seem to improve the efficacy significantly when compared with approved lower dose (25 mg b.i.w or 50 mg q.w. for etanercept and 50 mg q4w for golimumab). For drugs like secukinumab, tofacitinib, and sarilumab, the maximum effect was also not detected in the highest dose. However, this should be interpreted with caution. The reason for secukinumab may be that the dose-dependent response had been obscured by the i.v. loading regimen in MEASURE 1[17] and MEASURE 3.[18] The relatively short research duration might also be the reason as a more visible dose-response was seen in longer term efficacy in those trials. As for sarilumab and tofacitinib, the lack of dose response might be a result of small sample sizes.

Explanatory covariates were included to assess their impacts on the drug effects. Similar to the results of a phase III study,[21] our analysis suggests that patients with lower baseline BASFI are shown to have a higher ASAS20 response. In addition, female gender was found to experience more improvement in BASDAI and BASFI, which was consistent with the result from a national prospective observational study in the United Kingdom.[22] However, in contrast, most other observational studies suggested that female gender was associated with a significantly lower response.[23] The major difference between our analysis and those observational studies is that our identification of covariate is based on the relative drug effects, which may show different results from that based on the absolute treatment effects.[24] Besides, our results are based on an aggregation of individual data, but it may not indicate that our results are biased.[25] Overall, gender differences in treatment response are still

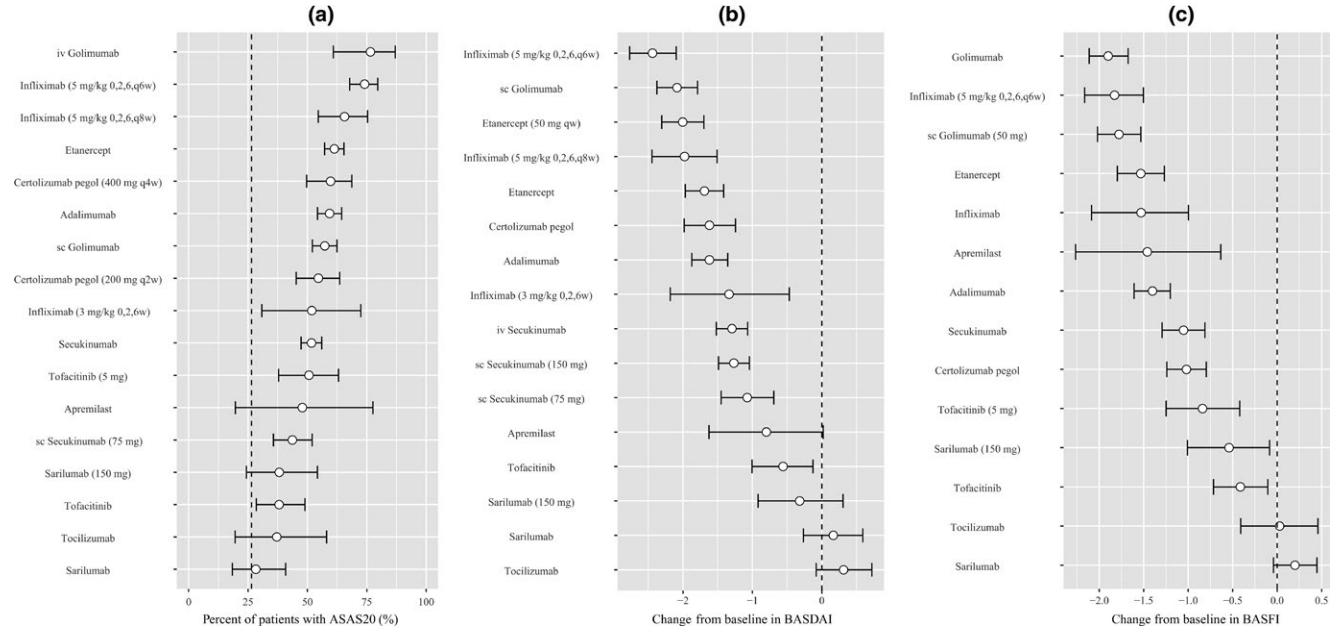

Figure 2 Ranking of treatments by placebo-corrected median response rate for ASAS20 (**a**), median change in BASDAI (**b**), and median change in BASFI (**c**) at week 12 (from high to low). Point estimates and 95% intervals were predicted from model simulation (N = 10,000), assuming a typical trial of 75% male patients with mean baseline BASFI value of 5.4. Dashed lines represent simulated placebo effect. For treatments with multiple regimens, only dosage regimens that had a different efficacy at week 12 are listed separately. ASAS20, ≥ 20% improvement in the Assessment of SpondyloArthritis International Society criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks; q6w, once every 6 weeks; q8w, once every 8 weeks.

a dilemma, and randomized clinical trials that are generated for examining the difference between genders may be required.[23]

Compared with the conclusions of previous meta-analyses, this study provided different and more detailed rank-order. The detailed comparison of outcomes is listed in **Table S1**. In addition to the four treatments (adalimumab, etanercept, golimumab, and infliximab) commonly reported in previous meta-analyses, six more (certolizumab, secukinumab, sarilumab, tocilizumab, tofacitinib, and apremilast) had been evaluated in this analysis. Moreover, regimens and doses that displayed different efficacy were estimated separately, whereas the traditional meta-analyses tended to assume them to have the same efficacy. Next, our study evaluated ASAS20, BASDAI, and BASFI values. The latter two have rarely been reported in previous studies. Furthermore, the inclusion of longitudinal profile also provided a new insight in the onset of drug efficacy in our study. Finally, our study had identified possible covariates that may influence the results.

There are some advantages of our meta-analysis. First, our analysis had the largest number of treatments, trials, and patients included. Second, using the longitudinal model, we are able to utilize all the time points to support the knowledge concerning a particular drug and, thus, a statistical difference may be detected. Third, because of the between-studies variability in population characteristics, design properties, as well as background treatments, it is inappropriate to estimate the placebo effect as a common comparator across all studies. Therefore, we estimate placebo effect for each study at each time point (nonparametric placebo model) to reduce the between-trial variability in an unbiased way. In addition, our inclusion criteria for double-blinded randomized controlled trials further reduced the remaining difference between arms in each study. Thus, we are able to focus only on the relative drug effects.

Still, there are some limitations in this analysis that remain to be addressed. First, we should note that trials of secukinumab included patients who had had no response to previous anti-TNFα.[17,26] This may be related to the lower relative response for secukinumab in our analysis. However, due to the fact that most studies included were TNF-naive and did not report the history of TNF usage, it is difficult to investigate the impact of the prior TNF experience. Second, efficacy data and the time course information included in this study were still inadequate for some treatments, resulting in the imprecise and unreliable estimates, particularly the E_{max} of apremilast, tofacitinib, sarilumab, and tocilizumab, as well as the efficacy onset of i.v. golimumab in the ASAS20 model and certolizumab pegol in the BASFI model. Therefore, caution is needed in interpreting the results.

In conclusion, the model-based meta-analysis provided a quantitative comparison of the efficacy of three classes of biologics and two classes of small molecules with a total of 10 drugs for three end points. The time course of all drugs for three end points was compared and efficacy measured by ASAS20 showed an immediate achievement of maximum effect for most drugs. Baseline BASFI scores and gender may identify the patients with higher drug efficacy. Further studies are still required to enhance the understanding of the relative drug efficacy.

Table 3 Final parameter estimates of ΔBASDAI and ΔBASFI model

End points	Drugs	Route (regimen)	Estimate	95% CI
ΔBASDAI		**E_{max}**		
	Adalimumab	s.c. (40 mg q2w)	−1.65	(−1.92, −1.39)
	Certolizumab pegol	s.c. (400 mg q4w) s.c. (200 mg q2w)	−1.66	(−2.03, −1.28)
	Etanercept	s.c. (50 mg q.w.)	−2.05	(−2.36, −1.74)
	Etanercept	s.c. (25, 50 mg biw)	−1.73	(−2.01, −1.44)
	Golimumab	s.c. (50, 100 mg q4w)	−2.13	(−2.43, −1.84)
	Infliximab (intercept)[a]	i.v. (5 mg/kg 0, 2, 6 q6w)	−2.43	(−2.78, −2.09)
	Infliximab. I(5-DOSE) (slope)[a]	NA	0.55	(0.15, 0.95)
	Secukinumab	s.c. (75 mg 0, 1, 2, 3, 4, q4w)	−1.09	(−1.49, −0.70)
	Secukinumab	s.c. (150 mg 0, 1, 2, 3, 4, q4w) i.v. (10 mg/kg q3w) i.v.-s.c. (10 mg/kg 0, 2, 4w followed by 75, 150, 300 mg q4w)	−1.30	(−1.53, −1.07)
	Sarilumab	s.c. (100 mg q.w.) s.c. (100, 150, 200 mg q2w)	0.17	(−0.28, 0.61)
	Sarilumab	s.c. (150 mg q.w.)	−0.32	(−0.95, 0.31)
	Tocilizumab	i.v. (8 mg/kg q4w)	0.32	(−0.09, 0.73)
	Tofacitinib	p.o. (2, 5, 10 mg b.i.d.)	−0.57	(−1.02, −0.12)
	Apremilast	p.o. (30 mg b.i.d.)	−0.82	(−1.67, 0.03)
	k_{AR}			
	Rate constant for onset of s.c. route	NA	0.33	(0.24, 0.45)
	Rate constant for onset of i.v. route	NA	0.83	(0.52, 1.30)
		Covariate		
	Percentage of male patients	NA	−0.72	(−1.50, 0.05)
ΔBASFI		**E_{max}**		
	Adalimumab	s.c. (40 mg q2w)	−1.44	(−1.65, −1.24)
	Certolizumab pegol	s.c. (400 mg q4w) s.c. (200 mg q2w)	−1.02	(−1.25, −0.80)
	Etanercept	s.c. (50 mg q.w.) s.c. (25, 50 mg biw)	−1.58	(−1.85, −1.31)
	Golimumab	s.c. (100 mg q4w) i.v. (2 mg/kg 0, 4, q8w)	−1.95	(−2.17, −1.74)
	Golimumab	s.c. (50 mg q4w)	−1.83	(−2.07, −1.59)
	Infliximab	i.v. (5 mg/kg 0, 2, 6 q6w)	−1.89	(−2.22, −1.55)
	Infliximab	i.v. (3 mg/kg 0, 2, 6 q6w) i.v. (5 mg/kg 0, 2, 6 q8w)	−1.58	(−2.16, −1.01)
	Secukinumab	i.v.-s.c. (10 mg/kg 0, 2, 4w followed by 75, 150 mg q4w)	−1.09	(−1.33, −0.84)
	Sarilumab	s.c. (100 mg q.w.) s.c. (100, 150, 200 mg q2w)	0.21	(−0.05, 0.46)
	Sarilumab	s.c. (150 mg q.w.)	−0.56	(−1.04, −0.08)
	Tocilizumab	i.v. (8 mg/kg q4w)	0.03	(−0.42, 0.47)
	Tofacitinib	p.o. (2, 10 mg b.i.d.)	−0.43	(−0.75, −0.10)
	Tofacitinib	p.o. (5 mg b.i.d.)	−0.87	(−1.30, −0.44)
	Apremilast	p.o. (30 mg b.i.d.)	−1.50	(−2.34, −0.65)
	$k_{general}$			
	Rate constant for the onset of all drug except for certolizumab pegol	NA	0.30	(0.22, 0.42)
	Covariate			
	Percentage of male patients	NA	−1.60	(−2.54, −0.66)

ΔBASDAI, change from baseline in Bath Ankylosing Spondylitis Disease Activity Index; ΔBASFI, change from baseline in Bath Ankylosing Spondylitis Functional Index; biw, twice weekly; CI, confidence interval; E_{max}, maximum drug effect; *k*, rate constant for the onset of drug effect; NA, not available; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks; q6w, once every 6 weeks; q8w, once every 8 weeks.

[a]The dose-response relationship of infliximab is linear with a slope and an intercept which is the maximum effect of infliximab 5 mg/kg 0, 2, 6, and q6w (i.e., the E_{max} of any dose of infliximab = infliximab (intercept) + infliximab (slope) * (5-dose)). For E_{max} estimates, in both the ΔBASDAI and ΔBASFI models, the larger the values are, the less effective they are.

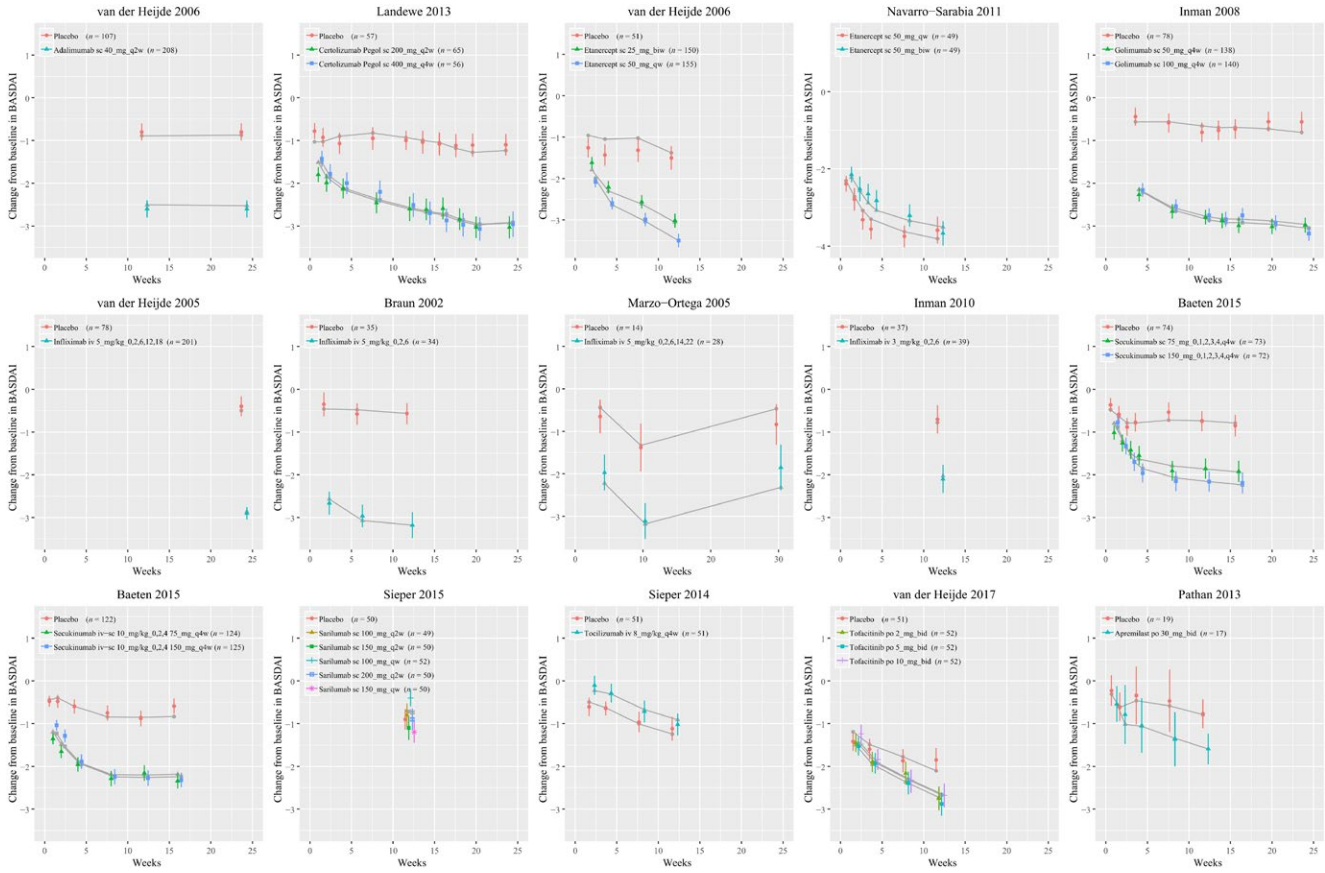

Figure 3 Model fitted time-course plots of change from baseline in BASDAI for representative trials. Color symbols and vertical bars are observed mean and standard error of time points; gray symbols and lines are the fitted values. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks. [Colour figure can be viewed at wileyonlinelibrary.com]

METHODS

Database development

A systematic search of clinical trials was conducted using PubMed, Cochrane, Embase, and ClinicalTrials.gov websites with the following keywords: adalimumab, certolizumab, etanercept, golimumab, infliximab, secukinumab, tocilizumab, sarilumab, tofacitinib, apremilast, ankylosing spondylitis, and randomized controlled trial. The cutoff date for the search was June 15, 2018. We also searched for possible articles from the reference lists of prior reviews.

All trials had to match the following criteria:

1. Double-blinded randomized clinical trials reported in English or Chinese.
2. Trials including patients with AS who were diagnosed based on the 1984 modified New York criteria.[27]
3. Patients were treated with biologics or small targeted molecules. Background treatments, such as NSAIDs, DMARDs, or oral steroids were allowed.
4. Trials reported at least one of following end points: ASAS20, ASAS40 (≥ 40% improvement in ASAS domains without any deterioration), ASAS5/6 (≥ 20% improvement in 5 of 6 ASAS domains, including spinal mobility and CRP), BASDAI, BASDAI50 (an improvement of ≥ 50% in BASDAI compared with baseline), BASFI, and Ankylosing Spondylitis Disease Activity Score.

Data were independently extracted by Yunjiao Wu and Xinying Feng with disagreements settled by Jiapeng Li. Only the data together with the control treatment were used for our analysis. Efficacy outcomes involving ASAS20, ASAS40, ASAS5/6, BASDAI, BASDAI50, and BASFI were extracted from articles as well as from tables and figures.

Normalization for different dose regimens was performed, for example, etanercept 25 mg b.i.w was standardized to etanercept 50 mg q.w. The BASDAI and BASFI scores, which were reported on a 0–100 scale or on a 0–10 scale in available trials, were converted into 0–10 range by dividing the 0–100 scale by 10. For continuous end points (BASDAI and BASFI), change from baseline (ΔBASDAI and ΔBASFI) was used in our meta-analysis, as change from baseline data could provide the least-biased estimate of a causal effect.[28] For trials in which efficacy end points were reported as postbaseline values, ΔBASDAI and ΔBASFI were derived from the difference between baseline values and postbaseline values. For continuous end points, missing SDs were imputed using the nonlinear mixed effects model.[29]

Model development

After graphical exploration of the data, the longitudinal profiles of all end points were fitted using hierarchical models with the method of maximum likelihood estimation. A nonparametric approach was implemented to model the data from the placebo arm at each time in each trial. To our knowledge, this approach allowed us to avoid misspecification of placebo effects and, thus, reduced bias.[28] All three models are listed as follows.

ASAS20 model

$$N_{\mathrm{ASAS20},ijt} \sim \mathrm{binomial}\left(N_{ij}, P(\mathrm{ASAS20})_{ijt}\right) \quad (6)$$

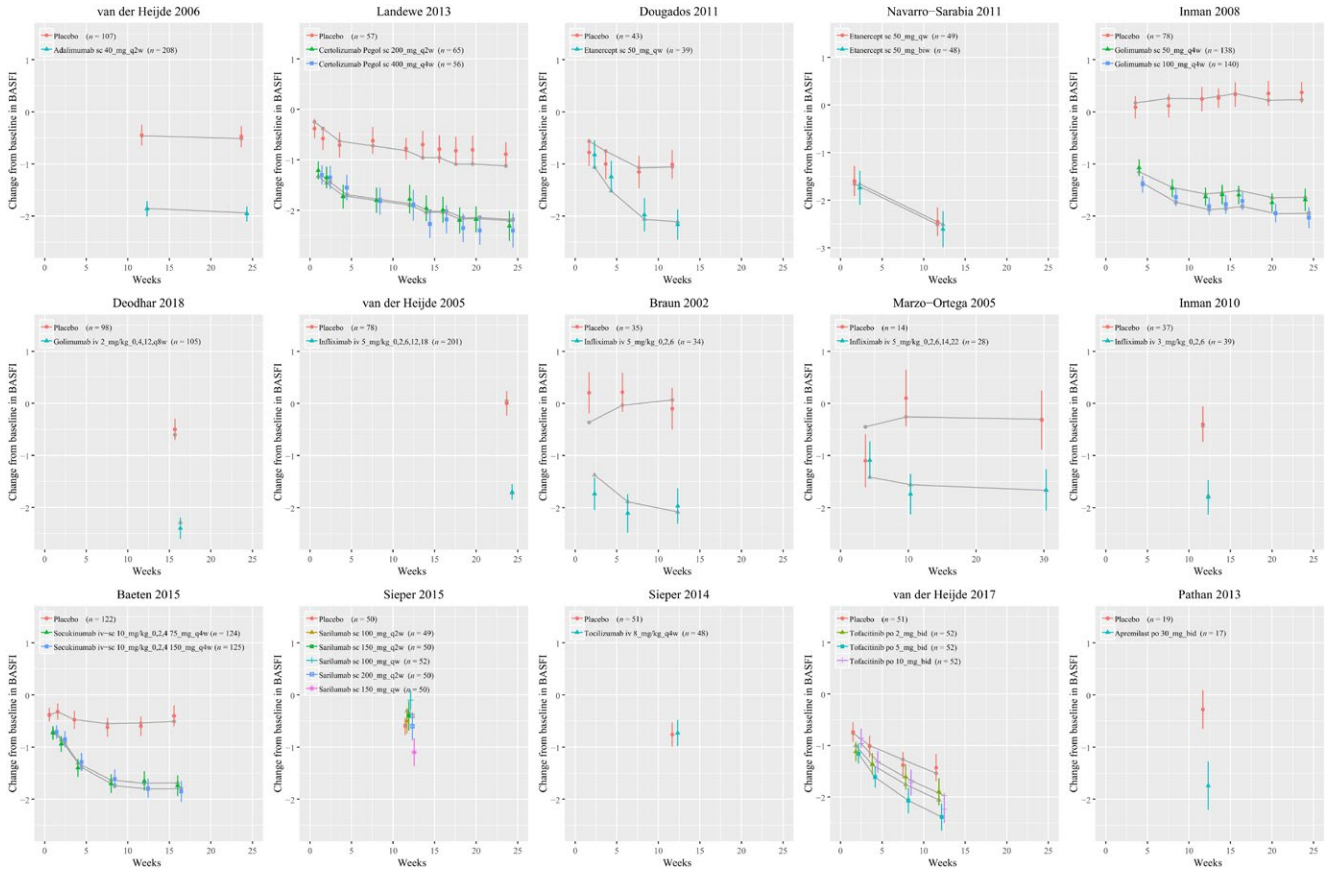

Figure 4 Model fitted time-course plots of change from baseline in BASFI for representative trials. Color symbols and vertical bars are observed mean and standard error of time points; gray symbols and lines are the fitted values. BASFI, Bath Ankylosing Spondylitis Functional Index; q2w, once every 2 weeks; q3w, once every 3 weeks; q4w, once every 4 weeks. [Colour figure can be viewed at wileyonlinelibrary.com]

$$P(\text{ASAS20})_{ijt} = g\left(E_{0it} + E_{\text{drug}}\right) \tag{7}$$

$$E_{\text{drug}} = f(\text{drug}, \text{dose}, \text{time}, \theta, X_{ij}) \tag{8}$$

Where $N_{\text{ASAS20},ijt}$ represents the number of patients achieving ASAS20 (≥ 20% in the Assessment of SpondyloArthritis International Society criteria[12]) at tth time in jth treatment arm of ith trial. It follows a binomial distribution with probability P (ASAS20) and sample size (N_{ij}).

The g is the inverse logit transformation to restrict the treatment effect, which is the sum of placebo effect (E_{0it}) at tth time in ith trial and the drug effects (E_{drug}) to probability scale of a range of 0–1. Drug effect (E_{drug}) is a function dependent on dose, time, fixed-effect model parameters θ, and trial covariates X.

Initially, the drug effects were set to be constant over time (not dependent on time). Then, if the model fit improved, the model was further developed by using an exponential model to incorporate time variable to describe the potential time-varying drug effect:

$$E_{\text{drug}} = E_{\max_{\text{drug}}} \cdot \left(1 - e^{-k \cdot \text{time}}\right) \tag{9}$$

Where $E_{\max_{\text{drug}}}$ represents the maximum response for each drug, the parameter k is the rate constant describing onset of drug effect, namely the rate to achieve $E_{\max_{\text{drug}}}$. We first estimated a shared parameter k for all drugs and then refined the model by separate k for each drug. If estimating k for each drug resulted into overparameterization or failure of minimization of model run, then, based on the diagnostic plots and model fits, tried to combine the k for drugs in the same class or the same administration route or just evaluated the k of the drugs that manifested different time course.

For drugs with varied doses, different dose-response relationship function forms were tested to define the best one. For those drugs with limited dose ranges or without noticeable dose-response, the dose ranges were either "lumped" (assumed to have the same efficacy) or "split" (to separately estimate each dose or regimen). However, the former could result into increasing heterogeneity and the latter may lead to inadequate use of information.[30] Therefore, this analysis integrated the two methods—we lumped all the dose/regimen together and then individually estimated the $E_{\max}$ of the doses or regimens that have different efficacy, if a better model fit was achieved.

Weight was introduced according to the standard error of fitted values.[31] The sample size (N_{ij}) in each arm of each trial ensured that more influence was imposed by the larger studies as shown in the following equation:

$$\text{Weight} = \sqrt{\frac{P(1-P)}{N}} \tag{10}$$

ΔBASDAI and ΔBASFI model

The descriptions of the ΔBASDAI and ΔBASFI models are similar to that of the ASAS20 model and is described as follows:

$$\Delta Y_{ijt} = E_{0it} + E_{\text{drug}} \tag{11}$$

$$\text{Weight} = \frac{\text{SD}}{\sqrt{N}} \tag{12}$$

where ΔY_{ijt} is the ΔBASDAI or ΔBASFI value at tth time in jth treatment arm of ith trial, and E_{0it} captures the placebo effect at tth time in ith trial. The definition and components of E_{drug} are exactly the same as in ASAS20.

Weight was based on the standard error of observed values.[10] The N was the number of patients in each arm.

Covariate model

Baseline characteristics with relative rich information (percentage of male, disease duration, age, BASDAI, BASFI, and CRP) were included in our model as covariates to investigate their association with the drug effects, as described in Eq. 13, where θ quantifies the relationship between covariate and treatment effect:

$$\text{Covariate}_{\text{effect}} = \frac{\text{Covariate}^{\theta}}{\text{mean(Covariate)}} \tag{13}$$

Additionally, the model included terms to describe the within-group autocorrelation structure. Different forms of correlation, such as compound symmetry, AR1, AR2 (an autoregressive process of order 2), and an autoregressive moving average, were tested.

Model selection was based on the log likelihood ratio at an acceptance P value of 0.05. The parameter estimates of the final model were used to sample a total of 10,000 model parameters to conduct model simulation of drug response at week 12 (typical duration of trials in AS) and to visualize the results (displayed as median and the 2.5th and 97.5th percentiles). All data exploration, model development, and evaluation were generated in Rstudio (v. 1.1.453) and R (v. 3.5.0) using the gnls function of package nlme (v. 3.1–137).

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. The diagnostic plots for the ASAS20, △BASDAI, and △BASFI model.
Figure S2. Model fitted time-course plots of ASAS20, ΔBASDAI, and ΔBASFI value for additional trials included. Color symbols and vertical bars are observed mean and SE of time points; gray symbols and lines are the fitted values.
Table S1. Comparison of our study and previous meta-analyses.
Data S1. Dataset for ASAS20, △BASDAI, and △BASFI model.
Supplementary Materials S1. References and information for all studies included in the model-based meta-analysis; code for ASAS20, △BASDAI, and △BASFI model.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.Z., Y.W., X.F., J.L., and X.W. wrote the article. L.Z., C.Y., and Y.W. designed the research. L.Z., C.Y., and Y.W. analyzed the data.

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