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

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I f at t e c a at e eff cac ta t f e e e t a e, a te a . U t , t e e at e eff cac f a e b c a a a e t e et at a t (AS) a e t, c ea . T e bject e f t t a t a t f te e at e eff cac a t e c e f a t eat e t ea e b t e A S t A e et St e e c te a 20 c e (ASAS20), c a e f ba e e at A S t D ea e Act t I e (ASDAI), a at A S t F ct a I e (ASFI). T e e e 34 b e-b e t a f 10 b c a a, ec e e c a 5,339 at e t t AS e e c e t a a . T ee at e at ca e, t a a et c aceb e t at e e e t e c be te e t a f e f t e ab et ee eff cac ea e . T e e t etecte f ca t ffe e ce a c e t eat e t , a f ab a ab e e f t a e t e e t eff cac e a e e e ac a, ea e .

A y osi sp o yji is (AS) is i m m ory r um j is- s pri m ri y t ri z y t i m m jo o t xi s e o O t r m i s t jo s i u p ri p r t ri js, - t si js, t ri or uv j is. I m i y e t p j e i t ir o i w j t pr v r t w 0.1% 1.4% o y.[2] T p r m u j t r py o AS i v o v s o s t r oi- j-i m m ory ru s (NSAIDs), o v jo sy t j is s m o i yi ir um j ru s (DMARDs), jo o - i s. NSAIDs r t irs ti ru s or AS, u tt r r s j s o m p j e w o o o t r sp o e o t m. DMARDs m y us j s o p ri r t ri js, u tt y s w o vi or t xi m i s t jo s.[3] F or t os w o i or ou o t e o r t NSAIDs, t us u t y .6 ( ).6 (u)12 (t)17.7 (r)-3.4 (i(r)0.5 ( )2..3

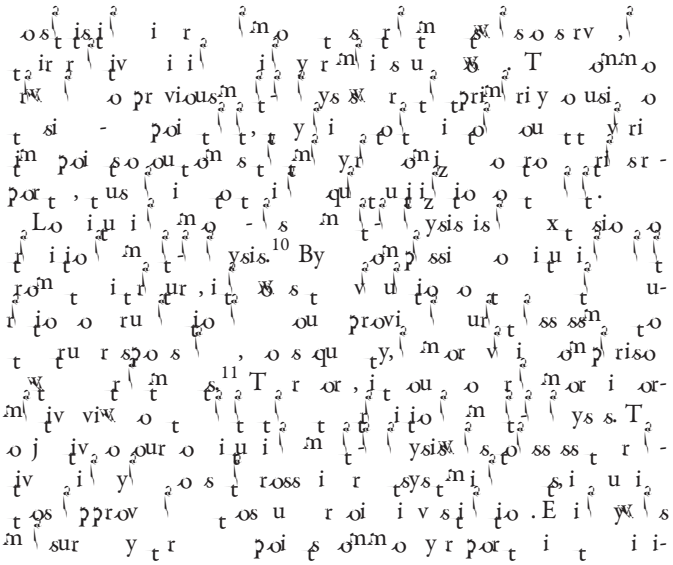

Table 1 Summary of available information for each drug in the analysis

D	T a

p r m trs r is t i **Table 3**. I t io o s m t s p r t *k* or ru i o t m prov t m o i t I s t , i i- i i r t t o s t s o o s t or i r t m i is t io rou t s. i t our v i rou t s (s. ., p.o., i.v., s. . t r i.v. o i r m (i.v.-s. .)[17,18], o m i t o s t o i.v. i.v.-s. . s i.v., s. . p.o. s s. ., us t t or p.o. r m r oo m i t ors p r t ysis.

I o t s t o t ASAS20 m o , r m i r i t o t r p s t t . Mor ov r, t r spo s o o - i t i 5 m i o t v ry m u ro m t o t r os o o i t i . T o s t or ru s y i.v. m j is t io rou t s (ET_{50} = 0.8 , ET_{90} = 2.8 s) ssi i i t y s t r t ru s y s. . rou t s (ET_{50} = 2.1 s, ET_{90} = 7.0 s; **Table 3**).

Am o t ov r t s i v s i t , o y t p r t o m p i t s i u s ov r t . T s m t ov r t p r m t r v u o −0.72 (−1.50, 0.05) i i t s t t m p - t i t r m or i y o s r t r m prov m t i BASDAI t m p t i t s.

T p r m t rs o t BASDAI m o r us o s m u- t p o jus t ro m s i i BASDAI s or s t 12, ssum i y p i t ri i t 75% m p i t t s (**Figure 2b**). S m i r o t r su t o t ASAS20 m o , TNF i - i i t ors r s i t m os t iv t t m t I ixi m 5 m / 0, 2, 6, q r su t i t r t s t p o- orr t (−2.46; CI = −2.80 t o −2.11) i BASDAI t 12, o y s. . o m u m (−2.11; CI = −2.41 t o −1.82) (s t r i v s i- i i.v. o m u m i o t r p or t BASDAI s or s). IL-6 i i i- t ors (s ri u m t o i z u m) i o t si i i t y m prov t BASDAI s or i t 95% CI rossi u .

ΔBASFI model

T orm u o ru t i ΔBASFI s s ri s :

For r t o i z u m p o,

$$\Delta BASFI = \quad max_{drug} \tag{4}$$

For o t r ru s,

$$\Delta BASFI = \quad max_{drug} \cdot \left(1 - \quad ^{- \quad general \cdot time}\right) \tag{5}$$

T i p r m t rs r is t i **Table 3**. T o s t o ru s (*k* r) s s t o t s m y u x p t r t o i z u m p o s i x i i t m m t t i m t o m xi m u m t . T m jori y o ru s, x p t r t o i z u m p o, iv ET_{50} t 2.3 s ET_{90} t 7.7 s.

T j usio o os r m m p t o t r p t i o t si i i t y m prov t m o . T t o i.v. o m u m s o t o s m t s p r t y s o y o p oi t s v i or t ΔBASFI m o . H v r, t i t o u t io o s p r t E_{max} p r m t r or s. . o m u m r m o 50 m q m prov t m o si i i t y, i i t t t t r i- m r t i t m prov m t o BASFI t s. . o m u m r m o 100 m q i.v. o m u m .

T p r t o m p i t s s o i u s ov r t . T s m t ov r t p r m t r v u o −1.60 (−2.54, −0.66) m s t t m p t r m or i y o s r t r m prov - m t i BASFI t m p t i t s.

T simul io o p or orr ΔBASFI, ssumi ypi ri w i 75% m p i sis s w i **Figure 2c**. I r v s o mum , r r sso m i is io rou s s r spo s i BASFI s mo r m s (−1.90; CI = −2.11 o −1.68), o w y i ixim 5 m / 0, 2, 6, q (−1.82; CI = −2.16 o −1.50). A pr m i s w s osi i i y m prov BASFI s or s (−1.46; CI = −2.25 o −0.64) w i r 95% CI.

Residual correlation

A r om p ri mo i u or r ssiv pro ss o or r 1 (AR1) w sus o ou or r si u orr io or ASAS20 mo , ΔBASDAI mo , ΔBASFI mo .

Model evaluation

T osi p o s or r mo s i o s w o vious miss p i i io (**Figure S1**). T mo - i im - ours p o s o r pr s iv ri s or r mo s r s w i **Figures 1, 3, and 4**, r sp iv y. T mo - i im - ours p o s or i- io ri s ou i **Figure S2**.

DISCUSSION

Our m ysis provi qu i iv m o or i- y omp riso ross 10 ru s. T r i r poi w r v u i is ysis. O is i ry poi (ASAS20) w o r o i uous poi s (ΔBASDAI ΔBASFI) ss ssi r spo s o r m (u io , p i o ss ssm i mm io), m pro y m i is s ivi y (i u , p i , s i ss) p ysi u io (i i y o p r orm op w i ivi i s o i y ivi). T ri- z io o r poi s w v u io o r r s o ru m p , us provi omp r siv u r- s i o ru i y. T p ysi i s p i s ou oos ir vor r m s p i o ir priori i s.

G r y, i y is simi r ross r m - sur s: i-TNF m w r mos iv r m s i ixim (5 m / 0, 2, 6, q) i.v. o m um provi i s r spo s . T w s i y w s o s rv i IL-6 i i i ors. T s r su s r suppor y - o op s u y,[19] omp ri i y o i ixim r p w o pr vious m - ys s,[5,7] i w i i r i y o i ixim w s . How v r, r w r si so m i r si r or r ross r poi s: pr m i- s r i ri BASFI i BASDAI ASAS20, w r s r o i z um p o r w ri BASFI.

Our o i u i mo - s m - ysis s- m io o ru o s G r y, i y m sur y ASAS20

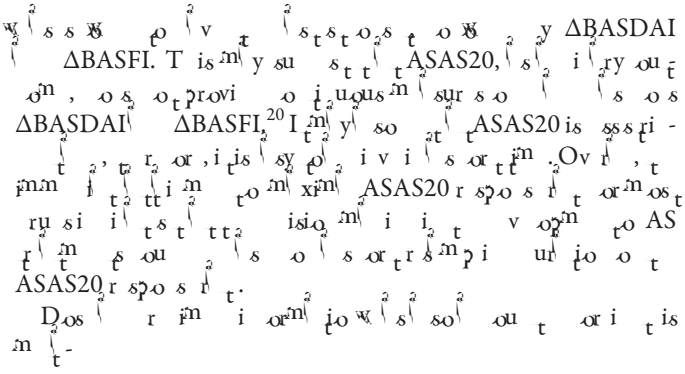

Figure 2 Ranking of treatments by placebo-corrected median response rate for ASAS20 (**a**), median change in BASDAI ( ), and median change in BASFI ( ) at week 12 (from high to low). Point estimates and 95% intervals were predicted from model simulation (N = 10,000), assuming a typical trial of 75% 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

Table 3 Final parameter estimates of ΔBASDAI and ΔBASFI model

E t	D	R te (e e)	E t ate	95% CI
ΔBASDAI		E_{max}		
	Adalimumab	s.c. (40 mg q2w)	−1.65	(−1.92, −1.)
	Certolizumab pegol	s.c. (400 mg q4w) s.c. (200 mg q2w)	−1.66	(−2.0 −1.28)
	Etanercept	s.c. (50 mg q.w.)	−2.05	(−2. , −1.74)
	Etanercept	s.c. (25, 50 mg biw)	−1.7	(−2.01, −1.44)
	Golimumab	s.c. (50, 100 mg q4w)	−2.1	(−2.4 −1.84)
	28/Span Actualg biw)	(-5.k5 (2)917.7FF00A 2-2.2 6778 2 54.2 (165)0.5 (2)-20.8 (.)-10.9 (1)-26.4 (TTw 1c 0 Tw 6.622 0 Td[(()22.5 (4)5		

Figure 3 Model fitted time-

METHODS

Database development

A sys m i s r o i i ri s o u usi Pu M , C o r , Em s , C i i Tri s. o si i t o i ... or s: i m u m , r o i z u m , t r o i m u m i ix- i m , s u i u m , o i i z u m , s ri u m , o i i , r m i s - y osi s o y i is, r o n i z o ro ri . T u t or s r s Ju 15, 2018. so s r or possi r i s ro n r r is o prior r vi s.

A ri s o m t t o i ri ri :

Do u - i r o n i z i i ri s r por t i E is or C i s.

Tri si u i i i AS r os s o 1984 m o i i N or ri ri .[27]

P i r r i ioo i s or s m r m o - u s. B rou r m s, su s NSAIDs, DMARDs, or o s ro i r .

Tri s r por t s o o o i poi s: ASAS20, ASAS40 (≥ 40% im prov m i ASAS o m i i ou y t rio io), ASAS5/6 (≥ 20% im prov m i 5 o 6 ASAS o m i s, i u i spi m o ii y CRP), BASDAI, BASDAI50 (im prov m o ≥ 50% i BASDAI o m r i s i), BASFI, A y osi S o y i is Dis s A ivi y S or .

D i p y x t y u ji o u i yi F i is r m s s tt y Ji p Li. O y t o r t i t o ro r m r us or our ysis. E i y ou o m s i v o vi ASAS20, ASAS40, ASAS5/6, BASDAI, BASDAI50, BASFI r x t ro m r i s s ro m s i ur s.

N or m i z io or i r os r m s s p r or m , or x m- p , t r p 25 m . s s t r i z o t r p 50 m . T BASDAI BASFI s or i r r p or o 0–100 s or o 0–10 s i i ri r o v r t i o 0–10 y ivi i t 0–100 s y 10. F or o i uous poi s (BASDAI BASFI), ro m s i (ΔBASDAI ΔBASFI) s us i our m - ysis s ro m s i ou provi t s i s s m o us t.[28] F or ri si i i y poi r r p or t s pos s i v u s ΔBASDAI ΔBASFI r riv ro m i r s i v u s pos s i v u s. F or o i uous poi s m issi SD r im pu t usi o i r m ix m o .[29]

Model development

A t r p i x p o io o t , t o i u i p roi s o poi r i tt usi i r i m o y i t m t o o m xi- m u m i i oo s im io . A o m ri p p ro s im p m t o m o t ro t p o r m t m i ri . T o our , is p p ro us o v oi m iss p ii io o p o , us, r u is.[28] A t r m o s r is t s o s.

ASAS20 model

$$ {}_{\mathrm{ASAS20},} \sim \mathrm{binomial}\left(\quad , (\mathrm{ASAS20}) \quad \right) \qquad (6)$$

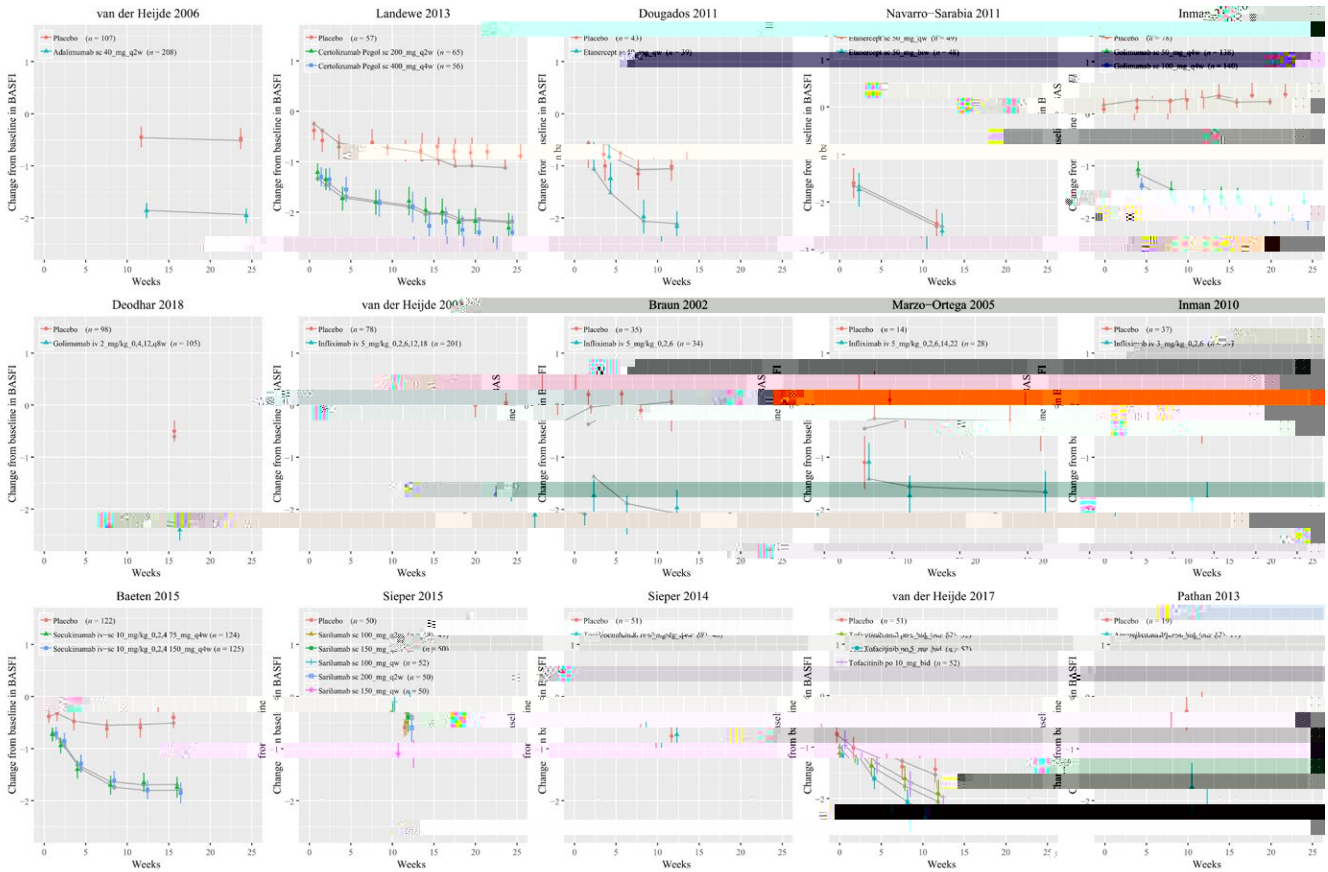

Figure 4 Model fitted time-course plots of change from baseline in BASFI for representative trials. Color symbols and vertical bars are observed mean and standard error of time points; gray symbols and lines are the fitted values. BASFI, Bath Ankylosing Spondylitis Functional Index; q2w, once every 2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

$$(\text{ASAS20}) = \left({}_{0} + {}_{\text{drug}} \right) \quad (7)$$

$$_{\text{drug}} = (\text{drug}, \text{dose}, \text{time}, \theta, \quad) \quad (8)$$

[illegible] $N_{\text{ASAS20},ijt}$ [illegible] ASAS20 (≥ 20% [illegible] Assessment [illegible] Spondyloarthritis [illegible][12]) [illegible] P (ASAS20) [illegible] (N_{ij}).

[illegible] (E_{0it}) [illegible] (E_{ru}) [illegible] 0–1. Drug [illegible] (E_{ru}) is [illegible] θ, [illegible] X.

[illegible]

$$_{\text{drug}} = {}_{\max_{\text{drug}}} \cdot \left(1 - {}^{-\,\cdot\text{time}}\right) \quad (9)$$

[illegible] $_{\max_{\text{drug}}}$ [illegible] k is [illegible] $_{\max_{\text{drug}}}$. [illegible] k [illegible]

k [illegible] k [illegible] k [illegible]

[illegible][30] [illegible]

[illegible][31] [illegible] (N_{ij}) [illegible]

$$\text{Weight} = \sqrt{\frac{(1-\ )}{}} \quad (10)$$

ΔBASDAI and ΔBASFI model

[illegible] ΔBASDAI [illegible] ΔBASFI [illegible] ASAS20 [illegible]

$$\Delta Y = {}_{0} + {}_{\text{drug}} \quad (11)$$

where ΔY_{ijt} is ΔBASDAI or ΔBASFI [illegible] E_{0it} [illegible] ASAS20.[10] [illegible]

Covariate model

[illegible] BASDAI, BASFI, [illegible] CRP) [illegible] Eq. 13, [illegible] θ [illegible]

[illegible] ARL, AR2 ([illegible] 2), [illegible]

[illegible] P [illegible] 0.05. [illegible] 10,000 [illegible] 12 ([illegible] AS) [illegible] 2.5 [illegible] 97.5 [illegible] R (v. 3.5.0) [illegible] (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.

Supplemental Material 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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