A Model Based Meta-Analysis for Bridging Treatment Doses of Rheumatoid Arthritis with Axial Spondyloarthritis

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Background

Anti-TNF, anti-IL17 and JAK inhibitors are the drug classes which have shown efficacy in both rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA). AxSpA includes radiographic and non-radiographic axSpA. The r-axSpA is also called as ankylosing spondylarthritis (AS). In general, wider dose range is studied in RA compared to axSpA. A model based meta-analysis (MBMA) has been conducted on summary level data with the purpose of bridging doses for the treatment of RA with axSpA. In particular, the objective was to compare the dose–response relationship for the efficacy endpoints ACR20 and ASAS20 for RA and AS respectively, and to assess the relative potency with the ultimate aim of supporting an expedite drug development of first in class compounds in a new indication (i.e. axSpA).

Methods

- **Database**: Certara's clinical trial outcome database for RA and AS was utilized [1]. In total 79 and 25 trials for RA and AS respectively with anti-TNF drugs (i.e. adalimumab, etanercept, golimumab, certolizumab and infliximab), anti-IL-17 drugs (i.e. ixekizumab and secukinumab) or JAK inhibitors (i.e. tofacitinib and filgotinib, Phase 3 data not included), as primary or comparator drug with placebo were included
- **Endpoints**: ACR20 and ASAS20 were analyzed using a nonlinear regression for binary endpoints, implemented in the generalized nonlinear least squares (gnls) and nonlinear mixed-effects (nlme) routines in R (version 3.6.1) [2].
- **Analysis**: Two step approach was adopted. First analysis included anti-TNF drugs which encompass majority of approved drugs in AS followed by combined analysis with three drug class.

The number of patients achieving response in the j^{th} treatment arm of the i^{th} study ($NACR20/ASAS20_{ij}$) was assumed to follow a binomial distribution according to the probability of the event $P(ACR20 \text{ or } ASAS20)_{ij}$ and the sample size N_{ij}.

Model 1

$P(ACR20 \text{ or } ASAS20)_{ij}$ was described as a function of a study specific placebo response and a dose–response relationship for the treatment effect:

$$P(ACR20)(Dose_{ij}) = logit^{-1}\left(E0_i + EMAX_{k\ ACR20} \cdot \frac{Dose_{ij}}{exp(ED50_{h\ ACR20}) + Dose_{ij}}\right)$$

$$P(ASAS20)(Dose_{ij}) = logit^{-1}\left(E0_i + EMAX_{k\ ASAS20} \cdot \frac{Dose_{ij}}{exp(ED50_{h\ ASAS20}) + Dose_{ij}}\right)$$

$E0_i$ represents trial specific placebo response which accounts for trial-to-trial variability. Maximum drug effect, Emax, was assumed same for drugs with the same mechanism of action k [2], but a separate Emax was estimated for each endpoint. Dose is the total daily/weekly/monthly dose normalized to the standard regimen for each drug, and ED50 is the dose required to achieve 50% of Emax and is estimated (in log domain) for each drug, h, and each endpoint,.

Model 2

$P(ASAS20)_{ij}$ was modified such that the ED50 for ASAS20 was derived by estimating an ED50 ratio between the two endpoints:

$$P(ASAS20)(Dose_{ij}) = logit^{-1}\left(E0_i + EMAX_{k\ ASAS20} \cdot \frac{Dose_{ij}}{exp(ER_k + ED50_{h\ ACR20}) + Dose_{ij}}\right)$$

where ER_k is the log of the ED50 ratio for the drug class k, by which ED50 of each drug varies between the RA and AS indications. An ER of 0 (i.e. exp(ER)=1) will indicate same dose-response for a drug class in RA and AS. Models were selected based on the model fit to the observed data, and likelihood ratio test.

Results

Analysis on anti-TNFs

Using Model 1, which allow estimate of separate ED50 for each drug across both indications, the ED50 for certolizumab was 10 fold higher for AS compared to RA (Table 1 Upper panel). This could be due to limited data for certolizumab in AS and comparatively higher placebo response in that trial. Excluding certolizumab data, both Model 1 and 2 described the observed data well (Figure 1) and the estimate of ED50 ratio, exp(ER), of 0.95 supports the concept of a similar potency for RA and AS indication (Table 1 Lower panel).

Analysis on anti-TNFs, anti-IL17 and JAK inhibitors

Model 2 applied to combined data (including certolizumab) showed point estimate of ED50 ratio, exp(ER), lower than 1 across three mechanisms, however the confidence interval of the log of the ED50 ratio, ER, includes 0 for all the three mechanisms (Table 2) supporting the pharmacological principle of a similar potency across the two indications. The conclusions of dose response relationship are relevant for both subtypes of axSpA since they share the same clinical features.

Conclusions

When agents with the same mechanism of action are efficacious in related diseases, there is an implicit assumption that dose-requirements are also similar. This is based on pharmacological principles that similar levels of target inhibition are required to elicit a clinical response due to similar pathophysiology. This MBMA supports this principle, and the evaluation of the same dose range in axSpA, without conducting a full dose ranging study, provided that the risk of the drug class not being efficacious in the new indication is appropriately discharged.

References

1. https://www.certara.com/data-and-informatics/codex-clinical-trial-outcomes-databases/
2. Mandema JW, Salinger DH, Baumgartner SW and Gibbs MA. A dose–response metaanalysis for quantifying relative efficacy of biologics in Rheumatoid Arthritis. Clinical Pharmacology & Therapeutics, 90 (6), 828-835 2011.

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Table 1. Model 1 results of aTNF class with Certolizumab (upper table) and Model 2 results without Certolizumab (lower table)

Parameter/Drugs	Regimen	Estimate	95% CI	Transformed value*	Estimate	95% CI	Transformed value*
Model 1		RA			AS		
$E_{max\ aTNF}$		1.78	(1.59 - 1.97)	0.72	1.91	(0.984 - 2.85)	0.74
ED_{50} adalimumab	SC q2w	3.01	(2.59 - 3.43)	20.3	3.15	(1.71 - 4.6)	23.3
ED_{50} etanercept	SC biw	1.30	(0.31 - 2.28)	3.7	1.64	(-1.4 - 4.67)	5.2
ED_{50} infliximab	IV q8w	0.0035	(-0.78 - 0.79)	1.0	-0.917	(-9.81 - 7.97)	0.40
ED_{50} certolizumab	SC q2w	3.47	(2.48 - 4.45)	32.1	5.41	(4.05 - 6.77)	223.6
ED_{50} golimumab	SC q4w	3.33	(2.64 - 4.01)	27.9	2.51	(-0.115 5.13)	12.3
Model 2		RA			AS		
$E_{max\ aTNF}$		1.66	(1.45 -1.86)	0.69	1.87	(1.38-2.36)	0.74
ED_{50} adalimumab	SC q2w	3.05	(2.57 - 3.52)	21.1	-	-	20.0
ED_{50} etanercept	SC biw	1.17	(0.104 - 2.23)	3.22	-	-	3.05
ED_{50} infliximab	IV q8w	-0.314	(-1.31 - 0.678)	0.73	-	-	0.69
ED_{50} golimumab	SC q4w	2.86	(2.04 - 3.69)	17.5	-	-	16.5
ED_{50} Scaling factor aTNF		-0.0559	(-1.28 - 1.17)	0.95	-	-	-

* For Emax: logit-1(E0+Emax) with $logit^{-1}$(E0)=0.3; for ED50 and ED50 Scaling factor, ER: exp(ED50) and exp(ER)

Figure 1. Model 1 (upper row) and Model 2 (lower row) Estimated vs. Observed Dose–Response Relationship (Excluding Certolizumab) for ACR20 and ASAS20 in Patients with RA and AS, Respectively

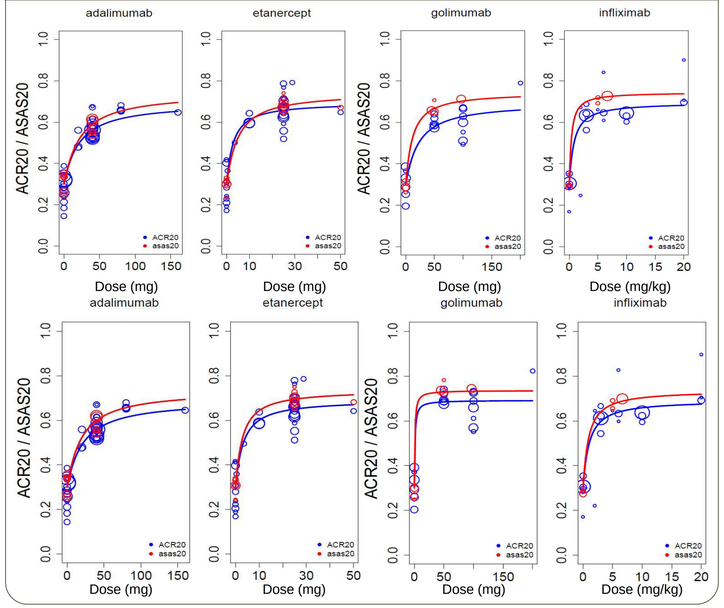
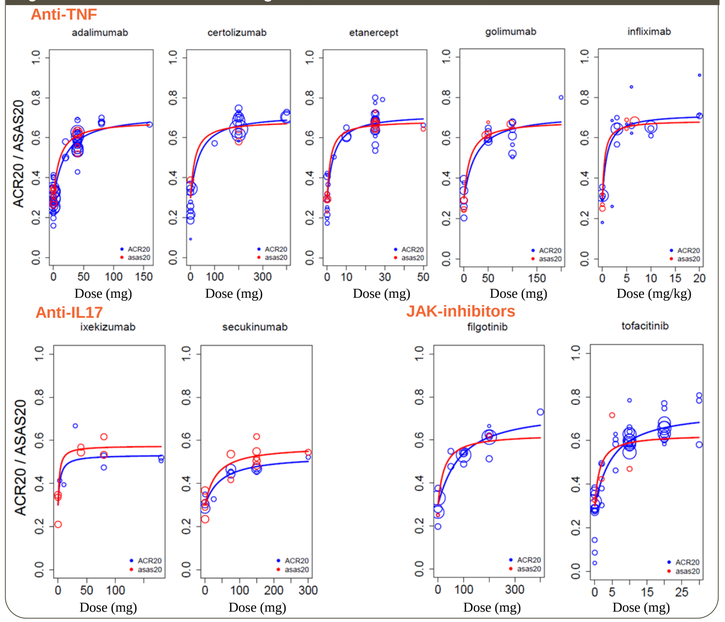


Table 2. Model 2 results including anti-IL17 and JAK inhibitors

Parameter/Drugs	Regimen	Estimate	95% CI	Transformed value*	Estimate	95% CI	Transformed value*
Model 2		RA			AS		
$E_{max\ aTNF}$		1.79	(1.6 - 1.98)	0.72	1.63	(1.22 - 2.03)	0.69
$E_{max\ aIL17}$		0.979	(0.369 - 1.59)	0.53	1.15	(0.737 - 1.56)	0.58
$E_{max\ JAKi}$		1.9	(1.62 - 2.18)	0.74	1.37	(0.467 - 2.27)	0.63
ED_{50} adalimumab	SC q2w	3.01	(2.61 - 3.41)	20.29	-	-	10.19
ED_{50} etanercept	SC biw	1.26	(0.285 - 2.24)	3.53	-	-	1.77
ED_{50} infliximab	IV q8w	-0.0528	(-0.85 - 0.745)	0.95	-	-	0.48
ED_{50} certolizumab	SC q2w	3.61	(2.74 - 4.48)	36.97	-	-	18.56
ED_{50} golimumab	SC q4w	3.19	(2.5 - 3.89)	24.29	-	-	12.19
ED_{50} secukinumab	SC q4w	3.76	(1.6 - 5.91)	42.95	-	-	29.99
ED_{50} ixekizumab	SC q2w	1.22	(-1.93 - 4.37)	3.39	-	-	2.37
ED_{50} tofacitinib	bid	1.66	(1.14 - 2.17)	5.26	-	-	1.34
ED_{50} filgotinib	qd	4.5	(4 - 5.01)	90.02	-	-	22.87
ED_{50} Scaling factor aTNF		-0.689	(-2.45 - 1.07)	0.50	-	-	-
ED_{50} Scaling factor aIL17		-0.359	(-3.73 - 3.02)	0.70	-	-	-
ED_{50} Scaling factor JAKi		-1.37	(-4.39 - 1.65)	0.25	-	-	-

* For Emax: logit-1(E0+Emax) with $logit^{-1}$(E0)=0.3; for ED50 and ED50 Scaling factor, ER: exp(ED50) and exp(ER)

Figure 2. Model 2 results including anti-IL17 and JAK inhibitors



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