

Characterisation of time course of response using model based meta-analysis of public domain data to support trial design in axial spondyloarthritis



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Background

- Axial spondyloarthritis (AxSpA) is a chronic inflammatory disease for which clinical response is assessed using binary endpoints like ASAS40 (common primary endpoint in registration trials) and continuous endpoints like BASDAI and back pain [1].
- Model-based meta-analysis (MBMA) utilises summary-level efficacy/safety data and provides quantitative framework for comparative assessment [2].
- Another application is the comparison of relative efficacy over time that can support early futility analysis, which is critical to make sure patients are not exposed to ineffective treatment.

Objectives

- Quantify the relationship between the magnitude of early (e.g. week 4 or 8) treatment effect and at later time points (week 16), as compared to placebo across different mechanisms of action.
- Use the modelled trajectory of the treatment effect over time to inform the design of a randomised controlled trial (RCT) in AxSpA and benchmark the operating characteristics (OCs) of an early futility analysis.

Methods

- Certara's clinical trial outcome database was used as data sources in the analysis [3].
- The dataset consisted of the time course of summary level ASAS40 response and BASDAI and back pain change from baseline from all active and placebo-controlled trials.
- The data were analysed using random effects meta-regression models. Different models for the onset of treatment effect relative to placebo were tested. This included no time course, exponential, sigmoidal onset or a nonparametric model.
- The covariates assessed were drug class, percent radiographic-AxSpA patients and TNF experience in total AxSpA population.
- Change in BASDAI score was analysed jointly with ASAS40. A scaling factor between the magnitude of treatment effect for the two endpoints was estimated. Effect of time and drug class on the scaling factor allowed different speed of onset between the endpoints and variation with drug class. A similar analysis strategy was used for the joint analysis of back pain and ASAS40.
- The simulations were performed using an exponential parametric placebo model and non-parametric treatment-time course models.
- The framework assessed the impact of different assumptions and design features on the OCs of an early futility analysis.

Results: MBMA

- A total of 42 RCTs (Table 1) that evaluated TNF (adalimumab, certolizumab, etanercept, golimumab, infliximab), IL-6 (sarilumab, tocilizumab), IL-17 (secukinumab, ixekizumab, bimekizumab), IL-12/23 (ustekinumab), and JAK inhibitors (tofacitinib, upadacitinib, filgotinib) were included.
- The treatment effect was estimated using a different fixed effect for every drug (E_{drug})
- A non-parametric model was used to estimate the onset of treatment effect. The fractional change in treatment effect relative to week 14-16 was estimated for week 1, 2, 3-4, 6-8, 10-12, and >17.
- Compared to week 16, ASAS40 response was on average significantly lower at week 1 (-59% [-95 to -53]), week 2 (-45% [-51 to -39]), week 4 (-36% [-42 to -30]), and week 8 (-8.4% [-16 to -0.5]) (Table 2).

Table 1. Summary of analysis set by drug class

	Placebo	IL-12/23 inhibitor	IL-17 inhibitor	IL-6 inhibitor	JAK inhibitor	TNF inhibitor	Total
Studies	40	2	9	2	3	27	42
Arms	40	4	20	6	5	33	108
Patients	3134	442	1963	302	307	2818	8966
*Indication	33118	2090	7092	2090	3060	20198	33118
r-AxSpA%	79	100	78	100	100	76	80
(0 to 100)	(0 to 100)	(0 to 100)	(0 to 100)	(0 to 100)	(0 to 100)	(0 to 100)	(0 to 100)
*TNF group	21228	191	1862	0	0	0822	21228
Prior TNF %	11	50	25	0	3.2	1.9	8.7
(0 to 100)	(0 to 100)	(0 to 100)	(0 to 0)	(0 to 5)	(0 to 17)	(0 to 100)	(0 to 100)
Baseline	6.5	7.5	6.9	6.6	6.7	6.4	6.5
BASDAI	(4.9 to 7.5)	(7.4 to 7.6)	(6.3 to 7.5)	(6.6 to 6.6)	(6.3 to 6.9)	(5.4 to 7)	(5.2 to 7.5)

*number of trials with r-AxSpA, AxSpA, and nr-AxSpA

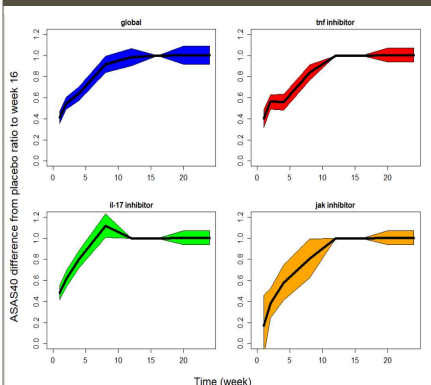
*number of trials with certain prior TNF experience

- There was a statistically significant ($p < 0.001$) mechanism by time course interaction with TNF and JAK inhibitors showing a slower onset compared to IL-17 inhibitors (Figure 1).
- There was marginal significance of prior TNF experience ($p = 0.048$) and no effect of % patients with r-AxSpA ($p = 0.45$) on the treatment effect.

Table 2. Parameter estimates for the global ASAS40 model with 95% CI representing the estimated treatment effect at week 16 (E_{drug}) and fractional change at other time points (k(t)).

Parameter	Value	CI low	CI high
E _{adalimumab}	0.264	0.213	0.315
E _{certolizumab}	0.385	0.321	0.449
E _{etanercept}	0.252	0.182	0.321
E _{golimumab}	0.275	0.217	0.333
E _{golimumab iv}	0.359	0.26	0.459
E _{infliximab}	0.352	0.274	0.429
E _{bimekizumab (Intercept)}	0.322	0.205	0.439
E _{bimekizumab (dose < 50 mg)}	-0.158	-0.296	-0.0198
E _{ixekizumab}	0.21	0.16	0.259
E _{secukinumab (Intercept)}	0.209	0.168	0.251
E _{secukinumab (frequency = "q4w")}	-0.0564	-0.118	0.00512
E _{secukinumab (dose < 80 mg & frequency = "wk 0.1,2,3,4 q4w")}	-0.0517	-0.15	0.0468
E _{filgotinib}	0.217	0.0889	0.365
E _{tofacitinib (Intercept)}	0.208	0.0677	0.349
E _{tofacitinib (dose < 5 mg)}	-0.0397	-0.192	0.112
E _{upadacitinib}	0.313	0.198	0.427
E _{sarilumab}	0.0447	-0.0418	0.131
E _{tocilizumab}	-0.0791	-0.222	0.0635
E _{ustekinumab}	0.0624	-0.00035	0.125
k(week1)	-0.589	-0.646	-0.532
k(week2)	-0.452	-0.512	-0.393
k(week3-4)	-0.36	-0.424	-0.295
k(week 6-8)	-0.0837	-0.162	-0.0054
k(week 10-12)	-0.0144	-0.096	0.0672
k(week >17)	0.00347	-0.0845	0.0914
Rho	0.692	0.637	0.74

Figure 1. Estimated time course of ASAS40 treatment effect relative to week 16 with 95% CI.



- Endpoints ASAS40, BASDAI and back pain are highly correlated. Scaling factors between endpoints are not impacted by time and drug class ($p = 0.065$) [data not shown].

Results: Trial Simulations and Futility OCs

- Using the modelled trajectory of the treatment effect over time (Table 3), an early futility analysis can be designed. For example, at week 4 the true treatment effect is expected to be 64% of the true treatment effect week 16. Assuming a certain true treatment effect Δ at week 16, the trial can be stopped if, for a given sample size S at interim and based on the observed trial data at week 4, the probability that the true treatment effect at week 4 being less than the corresponding expected target effect at interim is greater than the decision probability D .
- Trial simulations showed an early futility analysis can offer strong OCs (Figure 2, at $D = 90\%$ there is a 9.5% (resp. 62%) chance to stop the trial if the true week-16 ASAS40 effect is 20% (resp. 0%).
- Increasing the sample size could improve the OCs of the futility analyses but would trigger delay in decision-making (Figure 3).
- OCs were also robust across various assumptions on the speed of onset of the treatment effect and BASDAI or back pain did not offer any advantage compared to the ASAS40 (data not shown).

Figure 2. Probability to stop a trial based on week 4 ASAS40 data as a function of the true week 16 ASAS40 response and decision confidence threshold using a target effect of 12% at week 4 and 30 patients/arm at interim

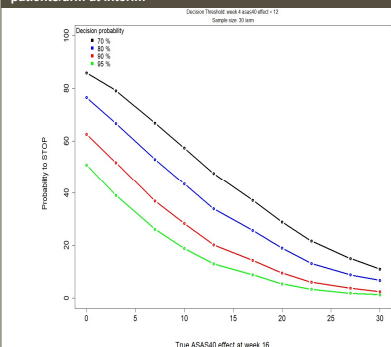
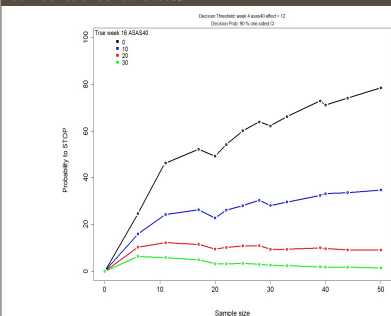


Figure 3. Probability to stop a trial based on week 4 ASAS40 data as a function of sample size at interim and the true week 16 ASAS40 response using a target effect of 12% at week 4 and decision confidence threshold of 90%



Conclusions

MBMA based on AxSpA public domain data enables to quantify the onset of treatment effect in different drug classes. Furthermore, it offers a quantitative understanding of the performance of decision criteria based on early clinical trial responses.

References

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Disclosures

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