Longitudinal model–based meta–analysis in rheumatoid arthritis: an application towards model based drug development

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Abstract

Aims

- Quantify longitudinal behavior of key clinical measure of signs and symptoms (ACR20) in rheumatoid arthritis (RA) over time and across drug treatment and patient population;
- Apply this knowledge in the decision making process for an internal Novartis compound, canakinumab.

Methods

- Summary level data was extracted from 39 phase II and III studies including data for all currently approved biologics (nine);
- The longitudinal meta-analysis model describes the full time course of ACR20 of all nine, currently approved biologics, standard of care (methotrexate) as well as true placebo across different patient populations.

Results

- Quantitative assessment of the efficacy observed in clinical studies of existing biological treatments in RA;
- The integrated analysis showed that the probability to be as good as the current most effective treatments in terms of the magnitude of effect was low, thereby supporting the decision not to progress canakinumab in RA.

Methods

Table 1. *Biological DMARDs currently approved in RA*

Drug name	Target	Approved dose/regimen	Way
Abatacept	CTLA4	500-1000mg (weight). Initial dose, dose at week 2, 4, then every 4 weeks	IV
Adalimumab	TNF	40mg every other week	SC
Anakinra	IL-1	100mg/day	SC
Certolizumab	TNF	400mg initially and at weeks 2 and 4, followed by 200mg every other week	SC
Etanercept	TNF	50mg per week. When administered as two 25mg injections, should be given either on the same day or 3 or 4 days apart	SC
Golimumab	TNF	50mg administered once a month	SC
Infliximab	TNF	3mg/kg followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 8 weeks	IV
Rituximab	CD20	two-1000mg intravenous infusions separated by 2 weeks	IV
Tocilizumab	IL-6R	every 4 weeks, starting dose is 4mg/kg followed by an increase to 8mg/kg based on clinical response	IV

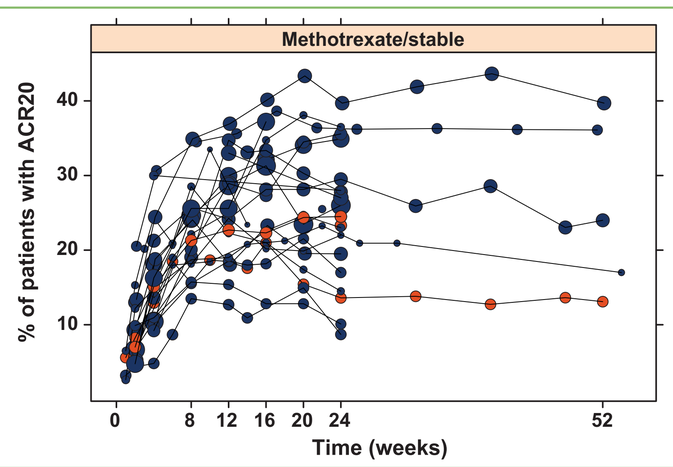
IV, intravenous infusion; SC, subcutaneous injection; CTLA4, Cytotoxic T-Lymphocyte Antigen 4; TNF, Tumor necrosis factor α; IL-1, interleukin 1; CD20, B-lymphocyte antigen CD20; IL-6R, interleukin-6 receptor.

The analysis included

- 39 phase II-III, double-blind, randomized, controlled clinical trials
- Longitudinal ACR20 responder rate, baseline characteristics, patient population, concomitant medications
- 73 treatment arms
- 12,000 patients
- 486 summary level data points

Large variation in placebo response across different studies was observed after adjusting for patient population.

Figure 1. *Heterogeneity in placebo methotrexate response across different studies*



This is an important feature of the data, which is acknowledged in the model for correct indirect comparison of different studies.

Nonlinear mixed effect model:

$$\text{logit}(y_{ilj}) = \text{logit}\left(\frac{\tilde{\phi}_{1k} t_{ij}^{\gamma_m \alpha}}{\exp(\theta_{2k})^{\gamma_m} + t_{ij}^{\gamma_m}}\right) + \varepsilon_{ilj}$$

$$\tilde{\phi}_{1k} = M \frac{\exp(\phi_{1k})}{1+\exp(\phi_{1k})}, \quad \phi_{1k} = \theta_{1k} + \eta_{1i} + \eta_{2il},$$

$$\eta_{1i} \sim N(0, \omega_1^2), \quad \eta_{2il} \sim N(0, \frac{\omega_1^2}{N_{il}}), \quad \varepsilon_{ilj} \sim N(0, \frac{\sigma^2}{N_{il}}).$$

Indices: i is the index over studies, l is the index for treatment-arm within a study, j is the index over time within a study. The index k represents therapy ID, which includes the drug, patient group and background therapy. Two different γ_m are estimated, one for biologics and one for placebo (index m). Offset of effect parameter α is fixed to 1 for all treatments except certolizumab and infliximab which share common fixed effect $\alpha < 1$.

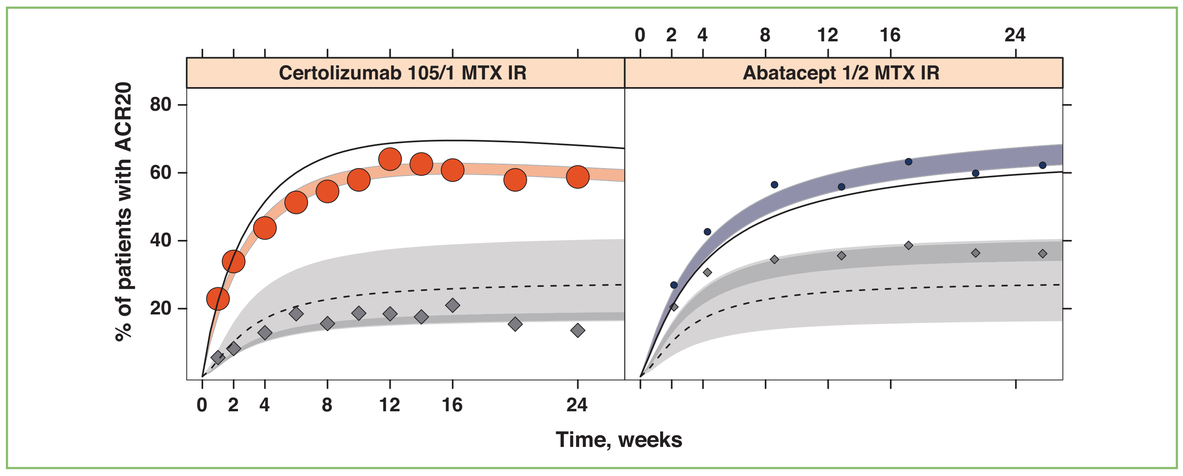
- Fixed effects: Emax - ϕ_{1k} (across different therapies); time course - θ_{2k} (across different drugs);
- Random effect parameters η_{1i} and η_{2il} represent BSV and BTAV, respectively.
- Residual unexplained variability ε_{ilj} as well as between treatment arm variability η_{2il} are adjusted according to the number of subjects in a treatment arm.

The model was fitted in WinBUGS using weekly informative priors.

Results

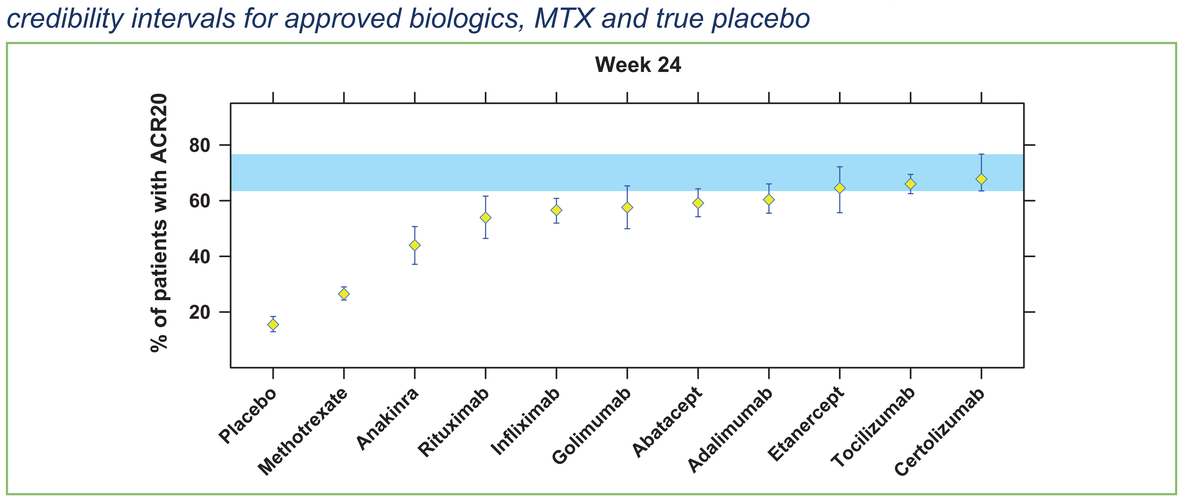
The concept of indirect comparison of different treatments is demonstrated in **Figure 2** with an example of two studies, one for certolizumab (1) (left) and one for abatacept (2) (right).

Figure 2. *Time course of ACR20 responder rate observed in two individual studies. Treatments are in combination with MTX, MTX IR patients*



Gray diamonds – the placebo methotrexate data, colored circles – data on active treatments, its size reflects the number of patients. Light grey areas - 90% model-based prediction interval for placebo MTX response across all studies. Dark grey areas and colored areas are model-based study level ACR20 for placebo MTX and active treatments respectively. Dash line is median placebo MTX response across all studies in this patient population. Solid lines are model-based predictions of the effect of active treatments in a hypothetical study in which placebo MTX response would be equal to median placebo response (dash line).

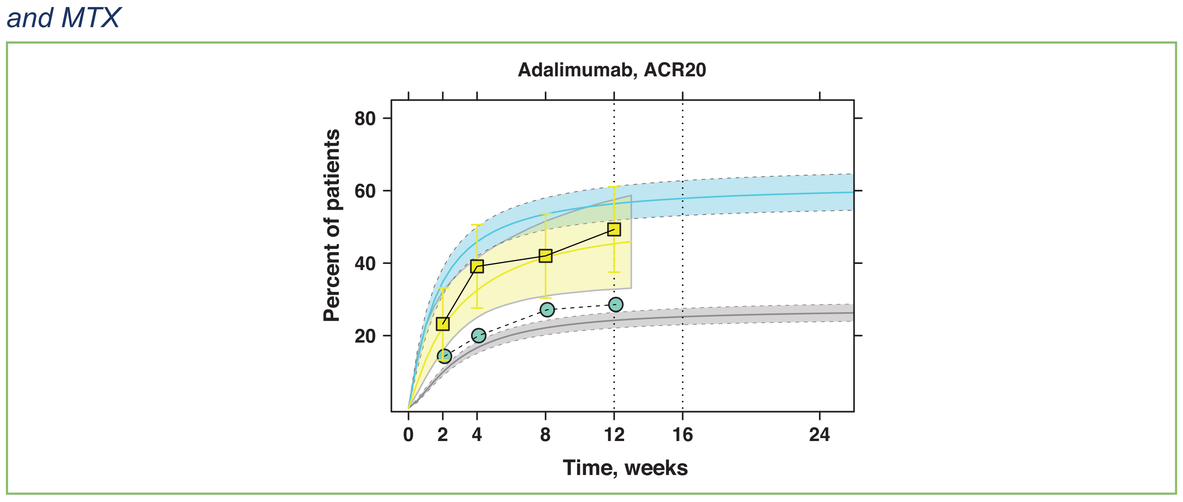
Figure 3. *Model-based predictions of median ACR20 responder rate together with its credibility intervals for approved biologics, MTX and true placebo*



All treatments are given in combination with MTX (except true placebo) to patients who previously used MTX.

Profiling canakinumab vs. adalimumab

Figure 4. *Model based time course of ACR20 for Humira® and MTX vs. canakinumab (yellow) and MTX*



Yellow vertical bars are confidence intervals for canakinumab, green circles – MTX placebo from canakinumab study. One can see smaller ACR20 for canakinumab across all time points. MTX placebo responder rate in this study is slightly above the median placebo response from the literature.

Conclusions and perspectives

- Meta analysis allows quantitative integration of both internal as well as external information. It increases quantitative knowledge about the longitudinal behavior of key clinical measures used in RA across patient population and background therapy.
- Meta analysis permits a valid indirect comparison of different studies adjusted by the placebo response.
- It allows "Benchmarking" internal compounds vs. competitors throughout drug development in terms of both time course and magnitude of effect as demonstrated in **Figure 4.**
- Integrated analysis supported the decision to stop the development of canakinumab in RA.
- Support optimal dose and regimen selection.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

References

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Poster presented at the Population Approach Group Europe (PAGE), June 7–10, 2011, Athens, Greece.