

Delineation of the treatment effect of methotrexate when used in combination therapy for rheumatoid arthritis

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Background

- Rheumatoid arthritis (RA) is a chronic autoimmune disorder that is characterised by inflammation in joint synovial membrane [1].
- For effective control of RA and hence the prevention of joint destruction, multiple drugs including the gold-standard treatment methotrexate (MTX) are used in routine clinical care.

Aims

- To determine whether it is possible to delineate the treatment effect of MTX in the presence of other RA treatments under an observational cohort study.

Methods

- The Early Arthritis Observational Study at Christchurch Hospital was established in 2004.
- Data on treatment history and disease activity score (DAS28) were available for 146 patients, and individual patients' treatment history ranged from 4 weeks to 8 years.
- In total 14 RA drugs were used and drugs excluding MTX were categorised based on the onset of action: rapid for corticosteroids and NSAIDs, intermediate with 1-4 weeks for biologic DMARDs, and delayed with 2-6 months for non-biologic DMARDs [2].
- Individual patients' treatment history in the observational study was extracted using MATLAB® (R2013b) and the time course of DAS28 was simulated based on the extracted treatment history.
- It was assumed that individual DAS28 ($DAS28_{ij}$) changed from the baseline ($DAS28_{0,i}$) due to both treatment effects (E_{ij}) and the natural history of disease (NH_{ij}) considering the measurement error (ε_{ij}), as given by

$$DAS28_{ij} = DAS28_{0,i} - E_{ij} + NH_{ij} + \varepsilon_{ij}.$$

- Here subscripts i and j represent the j th clinical visit in the i th individual. E_{ij} is considered to be nonlinear and additive, and NH_{ij} is linear [3].
- Model parameter values were derived from the observed data, the literature and opinions from clinical expert.
- A realisation of the study via simulation was assessed for similarities to the observed data comparing local polynomial regression (LOESS).
- Treatment effects of individual categories were explored under different study designs and were estimated through stochastic simulation-estimation (SSE) in NONMEM® 7.2. Specific study designs included to:
 - double the number of patients by replicating data records of the original study; and
 - increase the number of patients taking MTX alone from 2% to 20%.

Results

- After patients being stratified into high and low disease activity groups, the LOESS curves in observed and simulated DAS28 profiles had similar trends for both patient groups.

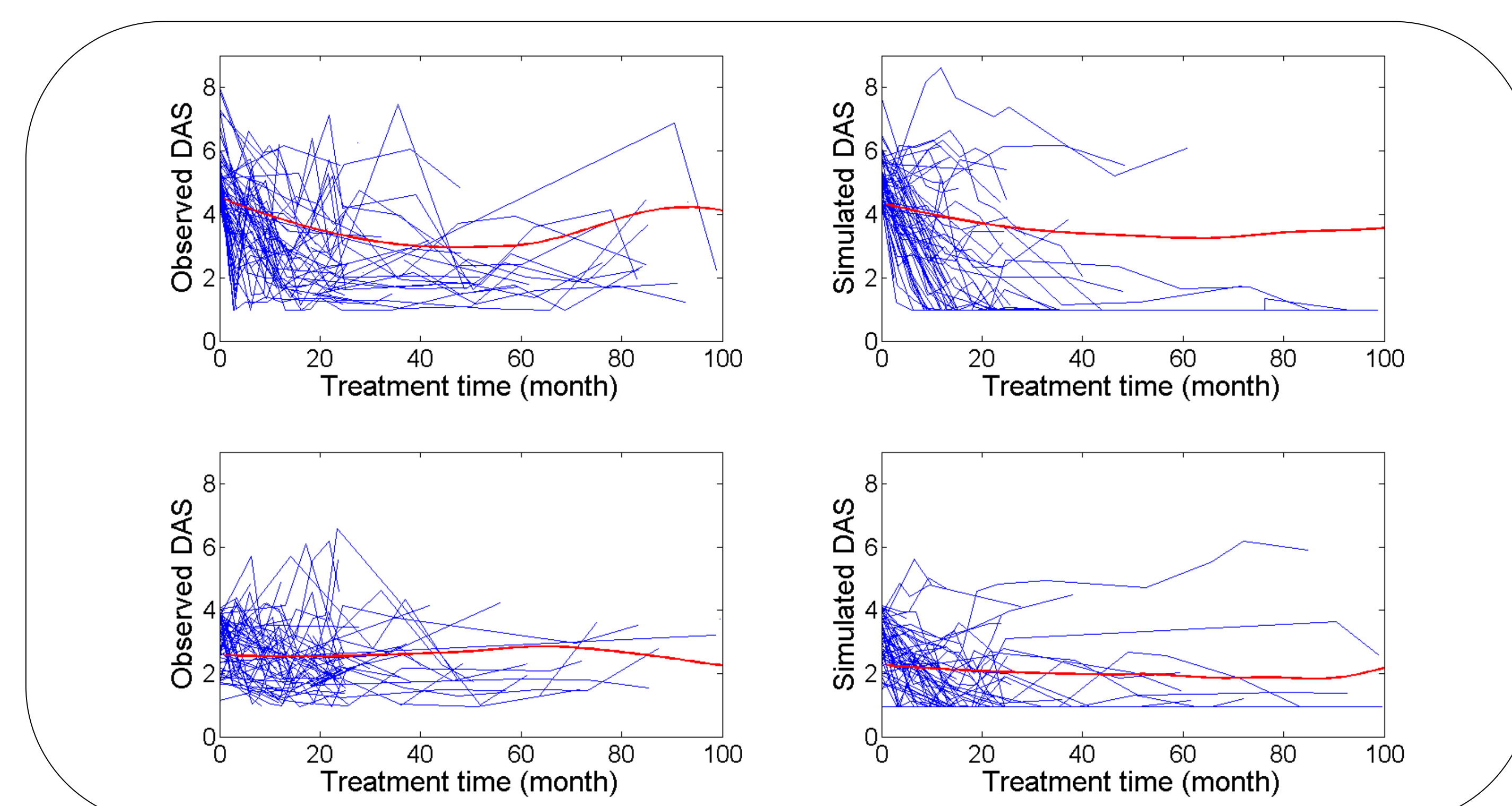


Figure 1: LOESS curves (red lines) in observed and simulated DAS28 profiles for high disease activity (top panels) and low disease activity (bottom panels) groups

- Under slow RA progression (0.01 per month for DAS28 increase), parameters pertaining to RA treatment effects were precisely estimated (refer to Table 1).
- A rapid disease progression (0.1 per month for DAS28 increase) confounded the treatment effects irrespective of study designs (results not shown).

Table 1: Parameter precision obtained from stochastic simulation-estimation (SSE) under slow disease progression

Parameters	Relative standard error (%)
MTX	6.7
Rapid onset of action	6.4
Intermediate onset of action	22.5
Delayed onset of action	10.2
Disease progression rate	60.0
DAS baseline	2.8
Measurement error (mean)	5.4
Measurement error (variance)	3.9

Conclusions

- Under the observational study design, MTX treatment effect was able to be delineated when the RA disease progression was slow.
- More complex and realistic simulation scenarios need to be explored in future studies to delineate and quantify the treatment effect of MTX when used in combination with other drugs in the management of RA.
- In future, a more mechanistic approach, e.g. population K-PD modelling, may be developed due to the absence of MTX PK data in the original observational study.
- Ultimately, it may be possible to learn about optimal MTX doses under observational cohort studies.

References

1. Cohen et al, *Arthritis Rheum* 2002;46(3):614-24

2. Bruce S. *Pharmacotherapy principles & practice* (2nd ed) 2013;p981-95

3. Holford N. *Br J Clin Pharmacol* 2015;79(1):18-27