



Inter-patient variability of local vs. systemic effects of TNF- α -neutralizing antibodies in rheumatoid arthritis

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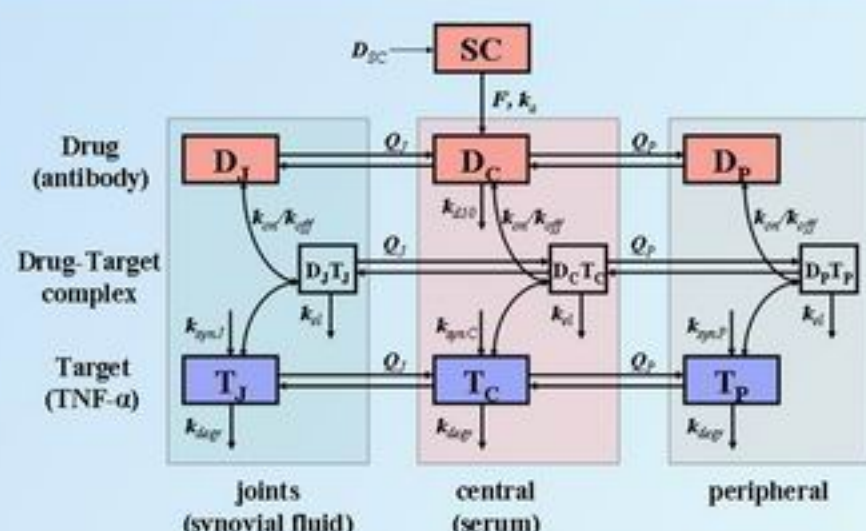
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BACKGROUND

Adalimumab, and other TNF- α -neutralizing antibodies that are used to manage rheumatoid arthritis (RA), can interact with TNF- α in the synovial fluid and in other locations in the body. The relative contribution of these local vs. systemic anti-TNF- α effects has been analyzed recently using a target-mediated drug disposition (TMDD) model with three sites of antibody-TNF- α interaction¹. This analysis has been based on the average data and did not take into account the inter-patient variability of the analyzed parameters.

METHODS

1. The PK-PD model of TNF- α and adalimumab¹

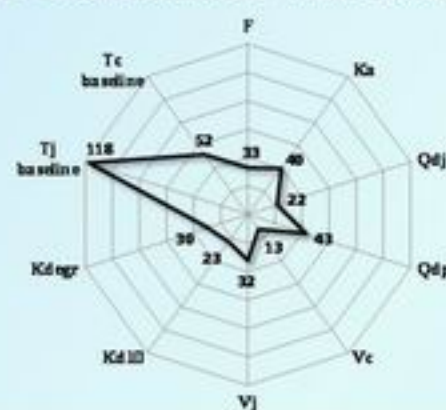


A recently published target-mediated drug disposition (TMDD) model with three sites of antibody-TNF- α interaction has been used in the simulations.

2. Parameters used in simulations

Process	Parameter	Definition	Value	Units
A	F	adalimumab SC bioavailability	0.64	-
	k_a	adalimumab SC absorption rate constant	0.030	h^{-1}
D	Q_j	permeation into joints	0.0422 (adalimumab) 0.00547 (TNF- α)	L/h
	Q_p	permeation into tissues	0.0482 (adalimumab) 0.0625 (TNF- α)	L/h
	V_c	central volume	2.95	L
	V_p	peripheral volume	2.53	L
	V_j	synovial fluid volume	0.30	L
	k_{deg}	adalimumab elimination rate constant	0.00431	h^{-1}
M/E	k_{deg}	TNF- α degradation rate	0.877	h^{-1}
	T_j baseline	baseline TNF- α levels in the joints	5.88	pM
disease state	T_c baseline	baseline TNF- α levels in the central compartment	4.47	pM
	k_{on}	association rate constant	6084	$\text{L}/\text{pmol}/\text{h}$
other	k_{off}	dissociation rate constant	0.170	h^{-1}
	k_{cl}	degradation rate of drug-target complexes	0.877	h^{-1}

3. Estimated variability parameters



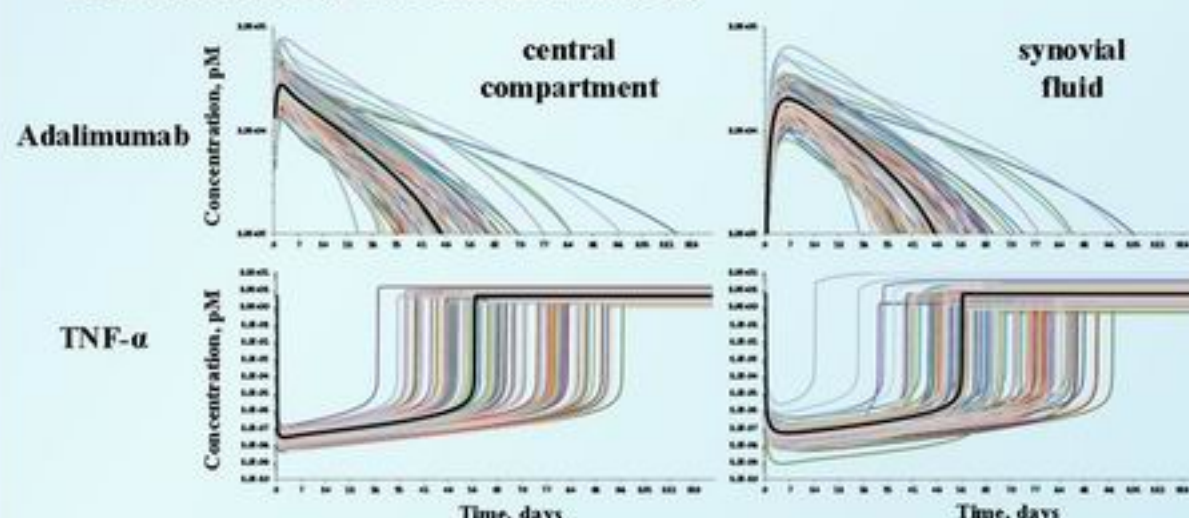
- The inter-patient variability data of the RA disease state and the pharmacokinetics of TNF- α -neutralizing antibodies were collected from the scientific literature.
- Variability of the individual parameters has been estimated assuming their lognormal distribution.
- The graph presents the %CV values of the major parameters.

OBJECTIVES

- To estimate the inter-patient variability in the rheumatoid arthritis (RA) disease state and in the pharmacokinetics and pharmacodynamics of TNF- α -neutralizing antibodies.
- To estimate the resulting variability in the time course of local (intraarticular) vs. systemic concentrations of TNF- α and in the efficacy of RA treatment.

RESULTS

4. The predicted variability of the TNF- α and adalimumab concentrations

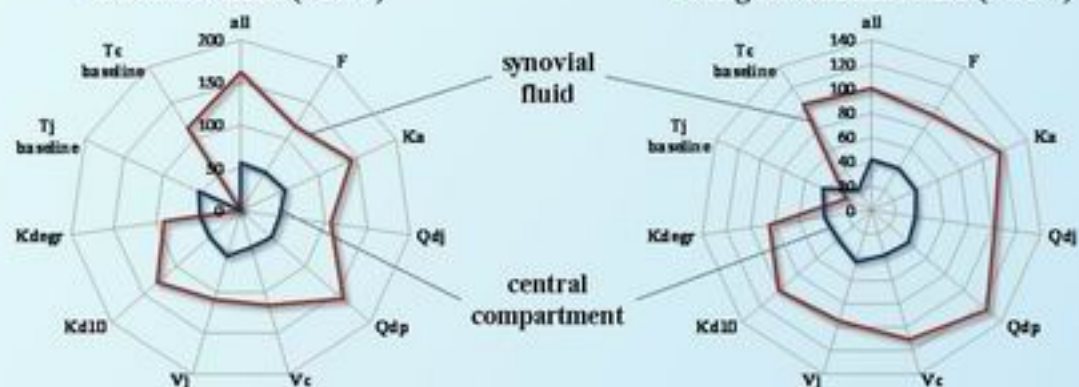


Based on the estimated variability sources, TNF- α and adalimumab concentrations were simulated for 100 patients. Black bold lines represent the simulation based on the mean parameter values.

5. The disease state is the major variability factor

Variability of the baseline TNF- α concentrations (%CV)

Variability of the anti-TNF- α effect of 40 mg SC adalimumab (%CV)

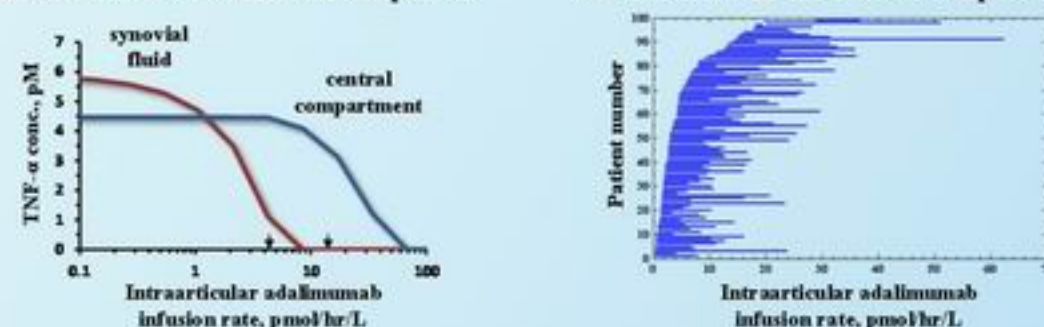


The graphs present the outcomes of simulations with excluded (set to zero) individual variability factors. The disease state (the baseline TNF- α secretion rates in the individual compartments) was the highest source of variability of the baseline TNF- α levels and anti-TNF- α effects.

6. Inter-patient variability of the optimal local delivery rate of adalimumab

Dose-response of intraarticular adalimumab in an individual patient

Therapeutic window of intraarticular adalimumab in the individual patients



Intraarticular adalimumab administration can lead to better balance of local vs. systemic anti-TNF- α effects (i.e., desired vs. adverse effects). The optimal rates of intraarticular adalimumab delivery vary substantially between the individual subjects.

CONCLUSIONS

- Despite the extensive clinical use of TNF- α -neutralizing antibodies, parameters that govern their efficiency in individual RA patients have not been identified yet.
- Simulations using the TMDD model with three sites of antibody-TNF- α interaction and the estimated variability parameters indicate that the disease state is the highest source of variability of the baseline TNF- α levels and adalimumab effects.
- Efficient RA treatment using TNF- α -neutralizing antibodies should take into account the inter-patient variability of local vs. systemic factors derived from the disease state.
- Correlation of local TNF- α levels in the affected joints with the clinical markers of RA warrants further investigation.
- Inter-patient variability should be taken into account for other drugs acting on soluble targets (growth factors, interferons, interleukins, immunoglobulins, etc.).

REFERENCES

- Stepensky D. Local vs. systemic anti-TNF- α effects of adalimumab in rheumatoid arthritis: pharmacokinetic modeling analysis of interaction between a soluble target and a drug. Clin Pharmacokinet 2012, in press