Is there a potential for therapeutic drug monitoring of subcutaneously administered tocilizumab in patients with rheumatoid arthritis in daily practice?

Sirs,

Tocilizumab (TCZ) is a recombinant humanised monoclonal antibody that inhibits the interleukin-6 (IL-6) inflammatory signalling pathway by binding to the soluble and membrane-bound IL-6 receptor (IL-6R) (1, 2). Overproduction of IL-6 has a multifactorial pathogenic role in anti-inflammatory diseases such as rheumatoid arthritis (RA), Castleman disease, and Crohn's disease (3). Moreover, immunogenicity seems to be less important factor in the pharmacokinetics and dynamics of TCZ (4). Currently, two formulations of TCZ are commercialised: intravenous (iv) and subcutaneous (sc). Both of them are approved for RA treatment with or without methotrexate (5, 6). Although Kneepkens *et al*. have shown high variability in iv TCZ serum drug concentrations (7), there is little data on the sc formulation. To date, the number of prescriptions of sc TCZ is expected to increase compared to iv TCZ since the sc formulation comes with several advantages; sc is preferred by a large proportion of patients over the iv formulation and it allows for a reduction in costs (8).

Previous studies have demonstrated an association between drug concentrations and therapeutic response in patients treated with iv TCZ. Frey *et al*. described that TCZ concentrations of 3.7 μg/ml result in 50% of the maximum treatment effect, measured by the Disease Activity Score 28 (DAS28) (9). Other authors demonstrated that CRP serum levels normalise when the TCZ concentration remains above 1 μg/ml[10]. This indicates that all IL-6Rs are bound to TCZ at concentrations above 1 μg/ml. Since a substantial proportion of patients have higher serum TCZ concentrations, it is likely that those patients are overexposed to the drug. Therefore, TCZ could be a potential candidate for therapeutic drug monitoring (TDM).

In an observational cohort study, we analysed patients who were diagnosed with RA according to the revised American College of Rheumatology 1987 criteria (11) and received treatment with sc TCZ. Treatment with TCZ was initiated in TCZ naive patients who had previously failed treatment with at least two disease-modifying anti-rheumatic drugs, including methotrexate. TCZ was subcutaneously administered with a standard regimen of 162 mg every week (12). Routine visits and blood sampling were scheduled at the initiation of treatment (baseline) and at weeks 4, 16, and 28.

Demographic characteristics (Table I) were collected. An enzyme-linked immunosorbent assay previously described (7) was used for drug level measurement. To obtain the concentration variability among patients at 28 weeks, the last observation carried forward (LOCF) was used. This was applied for patients in whom follow-up data were available for 4 and 16 weeks and not yet for 28 weeks.

In total, 21 patients were included in the study. Tocilizumab trough concentrations ranged from 4.6 μg/ml to 67 μg/ml, being highly variable at each time point between patients (Table II). Ninety percent of the patients showed stable serum drug concentrations after 16 weeks of treatment (Fig. 1), and around 95% of the patients had TCZ levels above 5 μg/ml. At 28 weeks, the overall mean ± SD TCZ concentration was 30.7±19 μg/ml. Data with and without LOCF were comparable (data not shown). The minimum concentration at 28 weeks was 5.6 μg/ml, the maximum concentration 63 μg/ml.

Considering the high inter-individual variability in drug concentration and the high cost of the therapy, TCZ could be a potential candidate for TDM. the limitation of our study is low patient number and not all the serum samples were available at week 28. However, more insight into the pharma-

Table I. Baseline characteristics (n=21).

Demographics	
age, years, mean ± SD	56 ± 11
gender, female, n (%)	16 (76)
BMI, kg/m^2, mean ± SD	27.5 ± 5.1
Disease status	
disease duration, years, median (IQR)	7 (5-13)
RF positive, n (%)	16 (76)
anti-CCP antibody positive, n (%)	14 (67)
CRP, mg/L, median (IQR)	4 (1-7)
ESR, mm/h, median (IQR)	11 (8-26)
DAS28, mean ± SD	4.3 ± 1.3
tender joint count, median (IQR)	5.5 (4-13)
swollen joint count, median (IQR)	3 (1-7)
VAS GDA patient, 0-100 mm, mean ± SD	49 ± 26
Pharmacological treatment	
prior treatment with biological DMARDs, n (%)	21 (100)
co-medication with methotrexate, n (%)	11 (52)
co-medication with prednisone, n (%)	6 (29)
other DMARD use (with or without MTX), n (%)	4 (19)

SD: standard deviation; BMI: body mass index; IQR: inter quartile range; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints; VAS: visual analogue scale in mm; GDA: general disease activity; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate.

Table II. Serum tocilizumab trough concentrations during the study period.

	Week 4	Week 16	Week 28
Patients on tocilizumab, n (%)	21 (100)	21 (100)	21 (100)
Samples, n (%)	19 (90)	17 (81)	10 (48)
Median tocilizumab conc., μg/mL, (min-max)	22 (4.6-42)	32 (4.9-67)	37 (5.6-63)
Patients with tocilizumab <5 μg/mL, n (%)	1 (4.8)	1 (4.8)	0
Patients with tocilizumab <1 μg/mL, n (%)	0	0	0
CRP, mg/L, median (IQR)	0 (0-2)	0 (0-1)	0 (0-1)

conc.: concentration; CRP: C-reactive protein; IQR: interquartile range.

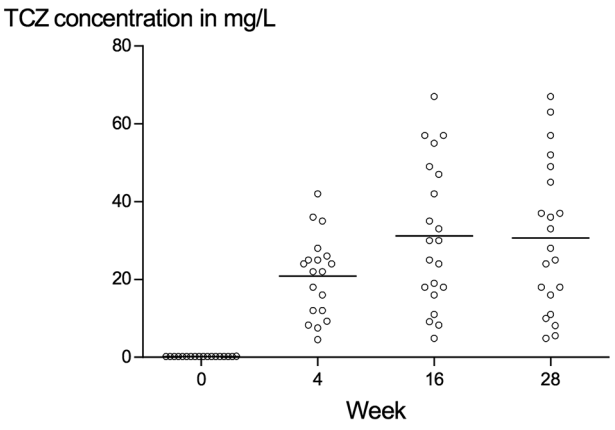

Fig. 1. Tocilizumab serum concentration at baseline, 4, 16 and 28 weeks, using last observation carried forward (LOCF) for data missing at 28 weeks (n=21 patients).

cokinetics and pharmacodynamics of TCZ is required. The minimum effective concentration of TCZ has not been identified yet. Therefore, we are currently conducting an RCT in a larger group of RA patients treated with TCZ, where we investigate concentration-guided dose reduction *versus* standard dosing.

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