Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis [DAR17/10/02]

Addendum #1

l'Ami et al. (2018)

21 January 2019

This addendum was produced in response to a request from the National Institute for Health and Care Excellence (NICE) Technical Team for an exploratory analysis considering a scenario where the drug dose in the standard care arm is not reduced (or reduced less than in the intervention [therapeutic drug monitoring, TDM] arm). This was requested as during scoping for the appraisal, the stakeholders indicated that dose reductions are currently not part of routine care in large parts of the UK. The NICE Technical Team requested that the Assessment Group (AG) considered using data from l'Ami et al. (2018).[1]

The study was identified in the searches for the clinical effectiveness systematic review but did not meet the inclusion criteria specified in the protocol, and was excluded on comparator because the physicians in the control arm had knowledge of drug and antidrug antibody levels in order to make their judgements.

The Assessment Group (AG) reviewed the study by l'Ami et al. (2018) to assess whether the requested analysis could be conducted based on data reported in l'Ami et al. (2018).[1] Although demonstrating the potential benefit of TDM, the study assessed the concentration-response relationship. The intervention described in the study was ADL dose-interval prolongation and not TDM. The AG considered there to be limited value in conducting a sensitivity analysis using the data from l'Ami et al. (2018) due to uncertainty. This was due to the following factors: median ADL dose at Week 28 was comparable to baseline in both groups, and the small sample size (approximately 50 participants).

A brief summary of the study by l'Ami et al. (2018) is presented below for information.

Study characteristics: l'Ami et al. (2018)

L'Ami and colleagues (201) reported clinical outcomes of a 28-week, open-label, randomised, parallel-group, non-inferiority trial performed in The Netherlands.[1] Adalimumab (ADL) serum trough concentrations were determined in people with RA who had been treated with ADL 40 mg every other week for at least 28 weeks and were not indicated for adjustment of ADL treatment, discontinuation or a scheduled surgery in the next six months; indicative of population stable on treatment. Participants were randomly assigned (1:1) to 40 mg ADL every three weeks (prolongation group) or to 40 mg ADL every two weeks (continuation group). The study population was followed up for 28 weeks.[1] The primary outcome was the change in disease activity score in 28 joints (ΔDAS28-ESR) after 28 weeks.[1] A ΔDAS28 of ≥0.6 was considered clinically relevant.[1] Clinical and laboratory assessments were scheduled at baseline, 12 and 28 weeks (Visits 1, 2 and 3, respectively) and AEs were monitored during follow-up.[1]

ADL serum trough concentrations measured by ELISA were previously described in Pouw and colleagues. The study was partially funded by the Dutch Arthritis Foundation.[1]

Baseline characteristics: l'Ami et al. (2018)

In total 147 participants were screened, 55 (37%) had an ADL concentration above 8 µg/mL. Of the 55 participants, 54 were randomised and 53 completed follow-up.[1] The majority of participants were female (93% and 96% in the prolongation and continuation groups, respectively).[1] The mean age of study participants was 60 years in the prolongation group and 58 years in the continuation group while the median disease duration was 11 years in both groups.[1] Concomitant treatment included methotrexate in most cases (>90%) and prednisolone in some cases.[1] The mean baseline DAS28-ESR score was 2.0 (SD ±0.8) and 1.6 (SD ±0.7) in the prolongation group and continuation group, respectively.[1] Median treatment duration with ADL was 6 years and 5.5 years, in the prolongation group and continuation group, respectively. Mean DAS-28 ESR at baseline was <2.6 denoting disease remission.[1-3] Participant baseline characteristics are summarised in Table 1.

Table 1: Description of participant baseline characteristics l'Ami et al (2018)

	Prolongation group[1]	Continuation group[2]
N	27	27
Age, mean ±SD years	60 (±10)	58 (±13)
Female, n (%)	25 (93)	26 (96)
BMI, mean ±SD	24.8 (±5.0)	23.8 (±4.3)
Prior biologic, n (%)	4 (15)	3 (11)
ADL treatment, median (IQR) years	6.0 (2.9-8.0)	5.5 (1.8-8.3)
MTX use, n (%)	26 (96)	25 (93)
MTX dose mg/week, median (IQR)	20 (15-21)	15 (10-20)
Disease duration, median (IQR) years	11 (8–18)	11 (6–19)
DAS28-ESR, mean ±SD	2.0 ±0.8	1.6±0.7

Key: ADL: adalimumab; BMI: body mass index; DAS28 = disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MTX: methotrexate; N: number of participants; SD: standard deviation

Notes:

1. Prolongation of the interval to ADL 40 mg once every 3 weeks
2. Continuation of the standard interval, ADL 40 mg every other week

Source: l'Ami et al. (2018)[1]

Disease activity score: l'Ami et al. (2018)

Mean DAS28 score at baseline was 2.0 (SD ±0.8) and 1.6 (±0.7) in the prolongation group and the continuation group, respectively. The difference between groups was calculated as -0.400 (95% CI -0.811 to 0.010; p=0.056). The mean change in DAS28 scores after 28 weeks was -0.14 ± 0.61 in the interval prolongation group and 0.30 ± 0.52 in the continuation group. The difference in mean change in DAS28 scores was 0.44 (95% CI 0.12 to 0.76; p = 0.01) in favour

of the prolongation group. Seven patients (26%) in the prolongation group versus 10 patients (37%) in the continuation group had an increase in DAS28 ≥0.6 points after 28 weeks (p=0.56).[1] Summary results are presented in Table 2.

Adalimumab concentrations: l'Ami et al. (2018)

In both groups mean ADL concentration decreased (Table 2); mean difference between the groups at week 28 was 2.6µg/mL (95%CI 1.2 to 4.1; p=0.001). In the prolongation group, the concentration decreased below 5µg/mL during 28-week follow-up in seven participants: one participant had an increase in DAS28 ≥0.6 and returned to standard dose.[1]

Table 2: Results: disease activity and adalimumab concentrations (l'Ami et al., 2018)

	Prolongation group[1]		Continuation group[2]		
	Baseline	**Week 28**	**Baseline**	**Week 28**	**Mean difference (95% CI) PG[1] vs CG[2]**
	N=27		N=27		
DAS 28, mean ±SD	2.0 ±0.8	1.9 ±0.7	1.6±0.7	2.0 ±0.9	
Mean ±SD DAS28 difference: BL vs Wk 28	-0.14 ±0.61 (N=27)		0.30 ±0.52 (N=24[3])		0.44 (-0.76, -0.12) p=0.01
	N =26		N=23		
ADL concentration µg/mL, mean ±SD	10.6 ±2.5	6.6 ±2.0	10.4 ±2.4	9.3 ±3.0	2.6 (1.2, 4.1) p=0.001

Key: ADL: adalimumab; CG: continuation group; CI: confidence interval; DAS28 = disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; N: number of participants; PG: prolongation group; SD: standard deviation; vs: versus; Wk: Week
Notes:
1. Prolongation of the interval to ADL 40 mg once every 3 weeks
2. Continuation of the standard interval, ADL 40 mg every other week
3. As reported in the paper
Source: l'Ami et al. (2018)[1]

Adverse events: l'Ami et al. (2018)

A total of 16 14 adverse events (AEs) were reported: two participants in the prolongation group and 12 participants in the continuation group. Of the AEs reported, respiratory tract infections were most common (occurring in three participants in the continuation group and two participants in the prolongation group). No serious adverse events were reported.[1]

Study conclusions: l'Ami et al. (2018)

The authors concluded that people with RA treated with ADL with trough serum concentrations above 8 µg/mL can prolong their dosing interval to once every three weeks without an increase in disease activity. In most participants the ADL concentration remained above 5 µg/mL

(concentration needed to block tumour necrosis factor). In the few patients where adalimumab concentrations decreased slightly below this level, it had no clinical consequences in the 28 weeks thereafter.[1]

References

1. l'Ami MJ, Krieckaert CL, Nurmohamed MT, van Vollenhoven RF, Rispens T, Boers M, et al. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: an open-label, non-inferiority, randomised clinical trial. Ann Rheum Dis. 2018;77(4):484-7.

2. Kiely P. The DAS28 score 2017 [cited 2018 01/11/18]. Available from: https://www.nras.org.uk/the-das28-score.

3. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S93-9.