

# Change in disease activity is associated with TNF- $\alpha$ inhibitor serum levels in patients with axial spondyloarthritis in daily clinical practice

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## Abstract

### Objective

To investigate, in daily clinical practice, TNF- $\alpha$  inhibitor serum trough levels in patients experiencing an increase in axial spondyloarthritis (ax-SpA) related symptoms. Secondly, to explore if these serum trough levels are associated with disease activity (DA) and/or change in DA.

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### Methods

Patients from the GLAS cohort treated with TNF- $\alpha$  inhibitors who had a serum trough level measurement during follow-up because of an increase in ax-SpA related symptoms between June 2015 and June 2018 were included. Serum trough levels were stratified in a therapeutic and below therapeutic range, based on published reference values of Sanquin in 2019. DA was assessed by ASDAS and BASDAI and change in DA (i.e.  $\Delta$ ASDAS or BASDAI compared to the visit before increasing symptoms).

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### Results

31 patients had a serum trough level measurement because of increasing symptoms. These patients had a median treatment duration of 4.8 years (IQR 0.9–8.6). 22 (71%) had active disease according to ASDAS (score  $\geq 2.1$ ) and 15 (47%) had therapeutic drug levels. The increase in DA was significantly larger in patients with below therapeutic drug levels compared to patients with therapeutic levels ( $\Delta$ ASDAS:  $0.94 \pm 0.81$  vs.  $-0.07 \pm 1.26$ ,  $p < 0.05$ ;  $\Delta$ BASDAI:  $1.72 \pm 1.73$  vs.  $-0.53 \pm 1.8$ ,  $p < 0.005$ ). No significant differences were found in absolute DA scores between patients with or without therapeutic drug levels.

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### Conclusion

In this observational study in daily clinical practice, approximately half of ax-SpA patients who experienced an increase in symptoms had below therapeutic TNF- $\alpha$  inhibitor serum trough levels. Change in DA and not absolute DA scores was significantly associated with drug levels.

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### Key words

ankylosing spondylitis, disease activity, disease activity score, tumour necrosis factor inhibitors

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## Introduction

Axial spondyloarthritis (ax-SpA) is a chronic auto-inflammatory disease which mainly affects the axial skeleton. If NSAIDs fail, tumour necrosis factor alpha (TNF- $\alpha$ ) blocking therapy is often the next step in treatment of active disease. However, approximately 50% of patients stop TNF- $\alpha$  inhibitor treatment after a period of time, mostly because of loss of efficacy (1, 2). Low drug levels of TNF- $\alpha$  inhibitors have been associated with lower capacity to neutralise TNF in RA patients and also therapeutic failure in RA and ax-SpA patients (3-5). Additionally, in approximately 30% of these patients antibodies against TNF- $\alpha$  inhibitors are detected, resulting in low serum trough levels and therapeutic failure (4, 6). Most studies included patients who recently started TNF- $\alpha$  blocking therapy. There are no data reporting on TNF- $\alpha$  inhibitor serum trough levels in case patients experience an increase in disease related symptoms during prolonged treatment in daily clinical practice in ax-SpA patients.

Therefore, our objective was to assess TNF- $\alpha$  inhibitor serum trough levels measured when patients reported an increase in ax-SpA related symptoms in daily clinical practice. Secondly, to explore if serum trough levels are related to clinical assessments including disease activity (DA) and change in DA.

## Methods

This study is a part of the Groningen Leeuwarden Ax-SpA (GLAS) cohort, which is an ongoing prospective longitudinal observational cohort study. Since November 2004, consecutive ax-SpA outpatients who started TNF- $\alpha$  inhibitors from the University Medical Center Groningen (UMCG) and the Medical Center Leeuwarden (MCL) are included. All patients fulfill the modified NY criteria or the ASAS classification criteria (7, 8). The GLAS cohort was approved by the local ethics committees of the MCL and UMCG and all patients provided written informed consent according to the Declaration of Helsinki.

In this observational study a large case series of patients embedded in the prospective GLAS cohort were included.

Patients had a cross-sectional serum trough level measurement during follow-up when they experienced an increase in ax-SpA related symptoms, defined as patient-reported worsening of back pain and/or stiffness, between the 1<sup>st</sup> of June 2015 and the 1<sup>st</sup> of June 2018. Patients were excluded from analyses if clinical assessments were >2 months apart from the TNF- $\alpha$  inhibitor serum trough level measurement (Fig. 1).

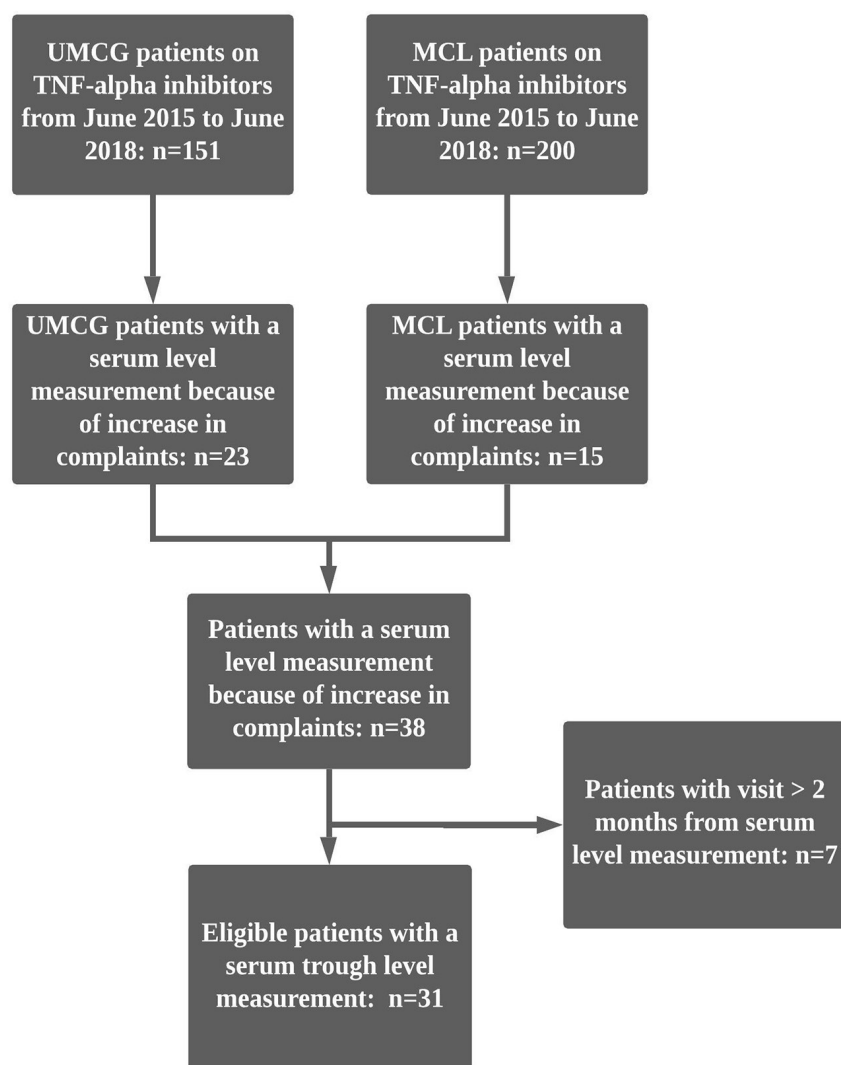
The prescribed TNF- $\alpha$  inhibitors were adalimumab, etanercept, infliximab and golimumab. Adalimumab (40 mg) was administered as subcutaneous injection on alternate weeks. Etanercept was administered as subcutaneous injection once (50 mg) a week. The standard regimen for infliximab in the GLAS cohort consisted of 5 mg/kg intravenously at 0, 2 and 6 weeks and then every 8 weeks. Golimumab (50 mg) was administered as subcutaneous injection once a month. Based on the opinion of the treating rheumatologist, the dosing regimen was adjusted in response to DA, side effects or co-morbidity.

Trough levels were defined as a measurement just before (at the same day or the day before) the next dose of TNF- $\alpha$  inhibitor. Trough serum concentrations were measured by enzyme-linked immunosorbent assay (ELISA: Sanquin, Amsterdam) (9). In order to be able to analyse all patients as one group, serum trough levels were stratified in a therapeutic and below therapeutic range, based on reference values published by Sanquin on their website until 2019 (10): adalimumab >5  $\mu$ g/ml, etanercept >2  $\mu$ g/ml and infliximab >1  $\mu$ g/ml. A cut-off level of golimumab is not yet definitely set by Sanquin, because of limited data. Their current estimate is >0.9  $\mu$ g/ml (11).

Patient characteristics and clinical DA assessments were measured as part of the standardised GLAS protocol. DA was assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and C-reactive protein (CRP). Cut-off values for high versus low DA were set as  $\geq 2.1$  and <2.1 for ASDAS,  $\geq 4.0$  and <4.0 for BASDAI  $\geq 5.0$  and <5.0 mg/L

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**Fig. 1.** Inclusion flowchart of GLAS patients with TNF- $\alpha$  inhibitor serum trough level measurements because of an increase in symptoms.

for CRP (12, 13). Change in DA ( $\Delta$ ASDAS,  $\Delta$ BASDAI,  $\Delta$ CRP) was defined as the difference in DA at the visit closest to the serum trough level measurement and the preceding DA assessment before patients experienced an increase in symptoms. In addition, Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Quality of Life (ASQoL) questionnaires were used to assess physical function and quality of life, respectively. For statistical analysis, Statistical Package for the Social Sciences (SPSS) v. 23.0 was used. Differences in patient characteristics and DA between patients with therapeutic and below therapeutic TNF- $\alpha$  inhibitor serum trough levels were assessed with independent samples t-test for normally distributed

data and Mann-Whitney U-test for non-normally distributed data. For dichotomous variables, the Chi-Square test or Fisher's exact test was used. The threshold for statistical significance was set at  $p < 0.05$ .

## Results

### Patient characteristics

Between June 2015 and June 2018, 351 ax-SpA patients from the GLAS cohort were treated with TNF- $\alpha$  inhibitors. In total, 38 patients had a serum trough level measurement assessed because of increasing symptoms, of which 31 patients had a GLAS visit within two months from the measurement. Of these 31 included patients, 25 had a diagnosis of AS and 6 of non-radiographic ax-SpA, 17 (55%) were male, mean

age was 47 (SD $\pm$ 12), mean symptom duration was 23 years (SD $\pm$ 14) and 22 (71%) were HLA-B27 positive (Table I). Median treatment duration with their current TNF- $\alpha$  inhibitor was 4.8 years (IQR 0.9–8.6). 12 patients received adalimumab, 10 etanercept, 7 infliximab and 2 golimumab.

### Drug levels and absolute scores of DA

Of the 31 included patients, 22 (71%) had active disease according to ASDAS  $\geq 2.1$ . According to defined cut-off values by Sanquin, 15 (47%) patients had therapeutic levels and 16 (53%) had below therapeutic levels. Median serum trough levels were therapeutic for adalimumab and infliximab and below therapeutic for etanercept and golimumab (Table II). In total, 58% of patients on adalimumab, 86% of patients on infliximab and 20% of patients on etanercept had therapeutic levels.

When excluding 8 patients with a higher or lower dose than standard, median serum trough levels were still therapeutic for adalimumab 5.2 (IQR 3.2–9.2) and infliximab 3.3 (IQR 0.8–5.8) and below therapeutic for etanercept 1.0 (0.6–1.9) and golimumab 0.3 (range 0.1–0.5).

Characteristics and clinical assessments of patients with therapeutic and below therapeutic TNF- $\alpha$  inhibitor serum trough levels are presented in Table I. Although not statistically significant, there were more patients with high DA according to ASDAS in the group with below therapeutic serum trough levels compared to therapeutic levels (93% vs. 67%,  $p = 0.139$ ). Moreover, no significant differences were found for other DA assessments, including cut-off values for high DA, and other clinical assessments including physical function (BASFI) and quality of life (ASQoL).

### Drug levels and change in DA

Change in DA was defined as the difference between the assessment before patients experienced an increase in symptoms and the assessment closest to the serum trough level measurement. Median duration between these 2 visits was 11 months (range 4–20). Increase in DA was significantly larger in patients with below therapeutic levels

**Table I.** Characteristics of 31 ax-SpA patients with serum trough level measurements stratified for (below-)therapeutic serum trough levels.

Patient characteristics	Total (n=31)	Therapeutic (n=15)	Below therapeutic (n=16)	p-value
Age (years)	47±12	49±12	45±11	0.342
Gender (male)	17 (55)	7 (47)	10 (63)	0.376
BMI (kg/m <sup>2</sup> )	27.0±5.7	27.5±6.6	26.6±5.0	0.658
HLA-B27-positive	22 (71)	12 (80)	10 (63)	0.326
Diagnosis of AS	25 (81)	11 (73)	14 (88)	0.394
Duration of symptoms (years)	23±14	24±15	22±13	0.758
History of EAM	12 (39)	8 (53)	4 (25)	0.149
History of peripheral arthritis	5 (17)	2 (13)	3 (19)	1.000
<b>Therapy</b>				
Current NSAID use	16 (52)	9 (60)	7 (44)	0.261
Current DMARD use	2 (7)	1 (7)	1 (6)	-
Previous use of TNF- $\alpha$ inhibitor (switch)	13 (42)	7 (47)	6 (38)	0.605
Duration since start current TNF- $\alpha$ inhibitor (months)	58 (11-103)	72 (22-134)	41 (9-93)	0.192
<b>Current TNF-<math>\alpha</math> inhibitor</b>				
Adalimumab	12 (39)	7	5	0.379
Etanercept	10 (32)	2	8	0.054
Infliximab	7 (23)	6	1	0.037
Golimumab	2 (7)	-	2	0.484
<b>Dose of TNF-<math>\alpha</math> inhibitor</b>				
Standard dose	23 (74)	10 (67)	13 (81)	0.433
Higher dose	2 (7)	1 (6)	1 (6)	0.742
Lower dose	6 (19)	4 (27)	2 (13)	0.394
<b>Clinical assessments</b>				
BASDAI (0-10)	4.7±1.9	4.4±2.3	5.0±1.5	0.376
ASDAS CRP	2.6±0.9	2.4±1.1	2.8±0.6	0.301
CRP (mg/l)	3.2 (1.7-6.0)	2.6 (2.0-5.6)	3.2 (1.3-7.0)	0.845
<b>Presence of active disease</b>				
ASDAS ( $\geq 2.1$ )	22 (71)	8 (67)	14 (93)	0.139
BASDAI ( $\geq 4.0$ )	21 (68)	9 (60)	12 (75)	0.458
CRP ( $\geq 5.0$ )	9 (33)	3 (25)	6 (40)	0.683
<b>Change in DA</b>				
$\Delta$ ASDAS	0.53±1.11	-0.07±1.26	0.94±0.81	<b>0.032</b>
$\Delta$ BASDAI	0.56±2.09	-0.53±1.8	1.72±1.73	<b>0.002</b>
$\Delta$ CRP	1.4 (-0.5-3.2)	1.7 (0.0-5.0)	0.50 (-2.0-3.1)	0.264
BASFI (0-10)	4.3 (3.4-5.8)	4.6±2.0	3.8 (2.1-5.8)	0.464
ASQoL (0-19)	9.0 (5.0-13.0)	9.4±5.8	8.0 (5.0-13.0)	0.690

Values are mean  $\pm$  SD, median (IQR) or n (%). Bold text indicates a significant p-value (<0.05)  
 SpA: axial spondyloarthritis; BMI: body mass index; HLA: human leukocyte antigen; AS: ankylosing spondylitis; EAM: extra-articular manifestations; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drug; TNF: tumour necrosis factor; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; CRP: C-reactive protein; DA: disease activity; BASFI: Bath AS Functional Index; ASQoL: AS Quality of Life questionnaire

**Table II.** Serum trough levels ( $\mu$ g/ml) in ax-SpA patients stratified for TNF- $\alpha$  inhibitors.

TNF- $\alpha$ inhibitor	Total (n=31)	Therapeutic (n=15)	Below therapeutic (n=16)
Adalimumab	6.0 (3.4-9.0)	8.5 (6.7-11.0) (n=7)	3.2 (2.5-4.2) (n=5)
Etanercept	0.8 (0.6-1.6)	2.9 (-) (n=2)	0.7 (0.5-1.2) (n=8)
Infliximab	3.2 (1.1-6.6)	3.3 (1.8-6.6) (n=6)	0.0 (-) (n=1)
Golimumab	0.3 (-)	-	0.3 (-) (n=2)

Values are median (IQR)

than in patients with therapeutic levels, for both  $\Delta$ ASDAS (0.94±0.81 vs. -0.07±1.26,  $p=0.032$ ) and  $\Delta$ BASDAI (1.72±1.73 vs. -0.53±1.8,  $p=0.002$ ), but not for  $\Delta$ CRP (0.50 (IQR -2.0-3.2) vs. 1.7 (IQR 0.0-5.0),  $p=0.264$ ).

## Discussion

In this observational study of ax-SpA patients TNF- $\alpha$  inhibitor serum trough levels were measured when patients experienced an increase in ax-SpA related symptoms. According to defined therapeutic and below therapeutic serum trough levels 16 (53%) patients had below therapeutic levels. When assessing the association between defined cut-off values for therapeutic and below therapeutic serum trough levels and DA, no significant differences were found for absolute DA scores and cut-off values. However, a significantly larger increase in DA ( $\Delta$ ASDAS and  $\Delta$ BASDAI) was found in patients with below therapeutic serum trough levels compared to patients with therapeutic levels.

In our study, only 20% of patients on etanercept had therapeutic serum trough levels. When excluding patients with a lower dose than standard this percentage was 14%. This gives rise to the question if patients are compliant to therapy or if cut-off values used to assess the therapeutic range are adequate, at least for etanercept. Sanquin has altered the advice of suggested cut-off values for etanercept on their website, after our study was conducted (10). For adalimumab the suggested therapeutic cut-off value is still  $>5 \mu$ g/ml and was based on a drug concentration-effect curve (14). In contrast, it has not been possible to generate cut-off values based on a drug concentration-effect curve for etanercept. Two studies, one in 292 rheumatoid arthritis (RA) patients and one in 162 ankylosing spondylitis (AS) patients showed median etanercept trough levels of 3.44  $\mu$ g/ml (IQR 2.34-4.78) and 3.0 (1.8-5.0) after 6 months, respectively. It was shown that 40% out of all non-responding RA patients had etanercept levels below 2.1  $\mu$ g/ml, and it was suggested that in these cases a dose increase might be assessed (15). In the second study, 35% of AS patients with active disease (ASDAS  $\geq 2.1$ ) had low etanercept levels of  $<1.80 \mu$ g/ml (3). These data suggests that therapeutic values of  $>2-3 \mu$ g/ml might be necessary in daily clinical practice. However, two studies in RA patients on etanercept showed mean serum trough levels of 1  $\mu$ g/ml after 8 weeks of therapy and me-

dian levels of 1.3  $\mu\text{g/ml}$  (IQR 1.4–3.3) after 12 months in patients with a good EULAR response (16, 17). These serum trough levels are more in accordance with median levels found in our study in patients who experienced increasing symptoms (0.75  $\mu\text{g/ml}$ ). These data show that a large range in ‘therapeutic’ etanercept trough levels is reported. Possible explanations for this might be differences in measurement methods, distribution volume and weight or change in pharmacokinetics over time. In contrast to patients on etanercept, 86% of patients on infliximab had therapeutic drug levels. Infliximab is given intravenously and the dosage is adapted to the weight of the patient, therefore different pharmacokinetics may play a role. Since infliximab is given as an intravenous bolus this may give wide fluctuations in serum concentrations, with studies reporting serum trough level concentrations ranging from 0 to approximately 28  $\mu\text{g/ml}$  (18). Also, intravenous drug admission promotes compliance (19).

In our study, serum trough levels were associated with change in DA but not with absolute DA scores. Other studies have shown associations between serum trough levels and absolute DA scores and DA cut-off values in ax-SpA patients. A prospective cohort study in 162 AS patients treated with etanercept showed that etanercept levels were significantly higher in patients with ASDAS < 2.1 (median 3.8  $\mu\text{g/ml}$ , IQR 2.5–5.2) compared to patients with ASDAS  $\geq$  2.1 (2.3  $\mu\text{g/ml}$ , 1.2–3.4) after 24 weeks of treatment (3). Another prospective cohort study in 115 AS patients recently started with adalimumab showed a longitudinal significant association between serum adalimumab level and DA over time with GEE analysis (4). One cross-sectional study in 62 RA and 81 SpA patients treated with TNF- $\alpha$  inhibitors for a median of 28 months showed a non-significant trend toward higher adalimumab and infliximab trough levels in patients responding to treatment, but not for etanercept (20). Most of these studies included patients who recently started anti-TNF- $\alpha$  therapy and had a treatment duration of 6 months to one year. In contrast, our

study included patients from daily clinical practice with a median treatment duration of 4.8 years and a self-reported increase in symptoms, since a flare definition was not yet available when this study was conducted. However, when assessing change in a standardised score for disease activity, patients with below therapeutic serum trough levels showed a clinically important worsening in ASDAS ( $\Delta$ ASDAS 0.94 $\pm$ 0.81) (21), whereas for patients with therapeutic levels this was not the case ( $\Delta$ ASDAS -0.07 $\pm$ 1.26). This is a useful finding for clinicians, since it has been shown earlier that, in daily clinical practice, validated ax-SpA disease activity assessments, such as ASDAS, are often not applied to evaluate disease activity and effectiveness of biological DMARDs (22).

The main limitation of our study was the relatively small number of included patients, since our study focused on patients who experienced an increase in symptoms during follow-up. It was not possible to calculate correlations between DA and serum trough levels since TNF- $\alpha$  inhibitor subgroups were too small.

In this observational study in daily clinical practice, approximately half of ax-SpA patients who experienced increasing symptoms during prolonged treatment with TNF- $\alpha$  inhibitors had below therapeutic drug levels according to cut-off values defined by Sanquin. For etanercept a valid concentration-effect curve has not been developed and therefore former published cut-off values are not reliable to use in daily clinical practice. More research is needed on the pharmacokinetics of different TNF- $\alpha$  inhibitor serum trough levels in relation to long-term therapy, weight or BMI, distribution volume and admission route. Change in DA and not absolute DA scores was significantly associated with serum trough levels. Therefore, we advise to apply a validated DA instrument such as ASDAS in daily clinical practice and to use the DA change scores instead of the absolute scores or cut-off values to evaluate efficacy of therapy. This will contribute to clinical decision making in the treatment of ax-SpA patients.

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## References

- ARENDS S, BROUWER E, EFDE M *et al.*: Long-term drug survival and clinical effectiveness of etanercept treatment in patients with ankylosing spondylitis in daily clinical practice. *Clin Exp Rheumatol* 2017; 35: 61-8.
- GARCÍA-LAGUNAR MH, GUTIÉRREZ-CÍVICOS MR, GARCÍA-SIMÓN MS *et al.*: Reasons for discontinuation and adverse effects of TNF $\alpha$  inhibitors in a cohort of patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Pharmacother* 2017; 51: 388-93.
- KNEEPKENS EL, KRIECKAERT CLM, VAN DER KLEIJ D *et al.*: Lower etanercept levels are associated with high Disease activity in ankylosing spondylitis patients at 24 weeks of follow-up. *Ann Rheum Dis* 2015; 74: 1825-9.
- KNEEPKENS EL, WEI JCC, NURMOHAMED MT *et al.*: Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow-up. *Ann Rheum Dis* 2015; 74: 396-401.
- BERKHOUT LC, VOGELZANG EH, HART MM *et al.*: The effect of certolizumab drug concentration and anti-drug antibodies on TNF neutralisation. *Clin Exp Rheumatol* 2020; 38: 306-13.
- GARCÉS S, DEMENGEOT J, BENITO-GARCIA E: The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: A systematic review of the literature with a meta-analysis. *Ann Rheum Dis* 2013; 72: 1947-55.
- ZEIDLER H, AMOR B: The Assessment in Spondyloarthritis International Society (ASAS) classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general: the spondyloarthritis concept in progress. *Ann Rheum Dis* 2011; 70: 2010-2.
- ARENDS S, BROUWER E, VAN DER VEER E *et al.*: Baseline predictors of response and discontinuation of tumor necrosis factor- $\alpha$  blocking therapy in ankylosing spondylitis: A prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011; 13(R94).
- ARENDS S, LEBBINK H, SPOORENBERG A *et al.*: The formation of autoantibodies and antibodies to TNF- $\alpha$  blocking agents in relation to clinical response in patients with ankylosing spondylitis. *Clin Exp Rheumatol* 2010; 28: 661-8.
- Diagnostic tests. Sanquin, Amsterdam. Available via: <http://www.sanquin.org/ml/producten-en-diensten/diagnostiek/diagnostische-testen/>. Accessed May 10, 2019.
- MARTÍNEZ-FEITO A, PLASENCIA-RODRIGUEZ C, NAVARRO-COMPÁN V *et al.*: Optimal concentration range of golimumab in patients with axial spondyloarthritis. *Clin Exp Rheumatol* 2018; 36: 110-4.
- MACHADO P, LANDEWÉ R, LIE E *et al.*: Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining cut-off values

- for disease activity states and improvement scores. *Ann Rheum Dis* 2011; 70: 47-53.
13. VAN DER HEIJDE D, RAMIRO S, LANDEWÉ R *et al.*: 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76: 978-91.
  14. POUW MF, KRIECKAERT CL, NURMOHAMED MT *et al.*: Key findings towards optimising adalimumab treatment: The concentration-effect curve. *Ann Rheum Dis* 2015; 74: 513-8.
  15. JAMNITSKI A, KRIECKAERT CL, NURMOHAMED MT *et al.*: Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. *Ann Rheum Dis* 2012; 71: 88-91.
  16. KEYSTONE EC, SCHIFF MH, KREMER JM *et al.*: Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004; 50: 353-63.
  17. CHEN DY, CHEN YM, TSAI WC *et al.*: Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 1-9.
  18. DE VRIES MK, WOLBINK GJ, STAPEL SO *et al.*: Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. *Ann Rheum Dis* 2007; 66: 1252-4.
  19. TRACEY D, KLARESKOG L, SASSO EH, SALFELD JG, TAK PP: Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008; 117: 244-79.
  20. ARSTIKYTE I, KAPLERYTE G, BUTRIMIENE I, VENALIS A, SHI G: Influence of immunogenicity on the efficacy of long-term treatment with TNF- $\alpha$  blockers in rheumatoid arthritis and spondyloarthritis patients. *Biomed Res Int* 2015; 2015: 7-9.
  21. MOLTO A, GOSSEC L, MEGHNATHI B *et al.*: An assessment in spondyloarthritis international society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. *Ann Rheum Dis* 2018; 77: 124-7.
  22. CHE H, ETCHETO A, DERNIS E *et al.*: Evaluation of collected outcome measures in axial spondyloarthritis in daily-care rheumatology settings: The experience of the RHEV-ER network. *Clin Exp Rheumatol* 2015; 33: 851-7.