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## Physical functioning in Ankylosing Spondylitis patients

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# **Chapter 4**

What do we miss?  
ASAS non-responders on  
anti-TNF therapy show  
improvement in performance-  
based physical function

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## Abstract

**Objective:** A prospective study was conducted in order to establish whether AS patients, who are defined as non-responders after 3 months of anti-TNF therapy, show improvement on performance-based tests of physical functioning.

**Methods:** At baseline and 3 months after the start of anti-TNF therapy, AS patients completed seven performance-based tests of physical functioning, questionnaires on self-reported physical functioning (BASFI) and disease activity (BASDAI), and a pain and a global patient assessment. The concordance between  $\geq 20\%$  intraindividual improvement on the performance-based test of physical functioning and (i) response to anti-TNF therapy [Assessment of SpondyloArthritis International Society 20% (ASAS20) response] and (ii)  $\geq 20\%$  intraindividual improvement on self-reported physical functioning (BASFI) was assessed.

**Results:** One hundred AS patients were included, of which 82 patients completed all tests at both time points. After 3 months of anti-TNF therapy, 27 (32.9%) patients were categorized as non-responders according to the ASAS20 response criteria. Improvement in performance-based physical functioning was seen in 13 of the 27 non-responders (48.1%) (i.e.,  $n=13/82=15.9\%$  of the total group). Furthermore, 30 (36.6%) patients showed no improvement on self-reported physical functioning (BASFI). However, 17 of the 30 (56.7%) patients did improve on the performance-based tests of physical functioning (i.e.,  $n=17/82=20.7\%$  of the total group).

**Conclusions:** After 3 months of anti-TNF therapy, performance-based tests of physical functioning showed improvement in 48.1% of the ASAS20 non-responders. With these performance-based tests, new information on outcome after anti-TNF therapy can be generated. Using performance-based tests alongside the BASFI could have additional value in the evaluation of outcomes for patients receiving anti-TNF therapy.

## Introduction

AS is characterized by limitations in physical functioning due to pain, stiffness and fusion of the spine. Anti-TNF therapy has been shown to improve physical functioning [1]. For evaluation of the disease course and the effectiveness of anti-TNF therapy, physical functioning is an important outcome measure.

Physical functioning in AS is most commonly assessed with the BASFI [2, 3], a self-reported, disease-specific, valid and reliable outcome measure [4-6]. In the absence of a true gold standard, the BASFI is considered the best option to assess physical functioning. However, it is a self-reported outcome measure and therefore is susceptible to subjective interpretation (under- or overestimation) due to confounding effects of perceived physical functioning, personality traits, pain, language or depression [7-10].

Performance-based tests are a more objective outcome measure to evaluate physical functioning. Performance-based tests of physical functioning based on the BASFI have been developed and have shown adequate to excellent reliability [11]. The association between the performance-based tests and the BASFI is only moderate [11, 12]. Furthermore, a previous study showed that alongside actual performance, AS patients seem to incorporate exertion and pain in their assessment of perceived physical functioning on the BASFI [12]. This suggests that performance and self-reported measures do not measure the same aspects of physical functioning. Consequently performance-based tests could provide an objective outcome measurement for the evaluation of physical functioning and give additional information on changes in physical functioning in addition to the BASFI. This would provide an argument for the use of performance-based tests alongside the BASFI in the evaluation of treatment modalities like anti-TNF therapy.

This prospective study therefore aimed to establish whether AS patients showed improvement on performance-based tests of physical function after 3 months of anti-TNF therapy (etanercept or adalimumab). We investigated whether patients, defined as non-responders according to the Assessment of SpondyloArthritis international Society 20% response (ASAS20) [13, 14], showed improvement in performance-based physical functioning. Furthermore, we investigated the differences between improvement in performance-based and self-reported (BASFI) physical functioning after 3 months of anti-TNF therapy.

## Patients and methods

Patients were recruited from a large outpatient centre for rheumatology and rehabilitation (Reade) in Amsterdam. Enrolment took place from May 2006 to June 2010. The following inclusion criteria were applied: diagnosis of AS according to the modified New York criteria [15],  $\geq 18$  years of age, eligible for treatment with anti-TNF and sufficient command of the

Dutch language. Patients were excluded if they had pulmonary, cardiovascular or neurological comorbidity affecting the patient's ability to perform daily activities. The study was approved by the medical ethics committee of Reade. All patients gave written informed consent according to the Declaration of Helsinki.

### *Measures*

At baseline and after 3 months of anti-TNF treatment (etanercept or adalimumab), patients completed seven performance-based tests of physical functioning, questionnaires on self-reported physical functioning (BASFI) and disease activity (BASDAI) [16], and a pain and patient global assessment. At both time points, spinal and hip mobility was also assessed, using the BASMI [17, 18].

Before each test the patient was uniformly instructed as to how to execute the test. The outcome of the performance tests was the time needed to complete the task, measured in seconds. A detailed description of the performance-based test was given in an earlier publication [11]. The performance tests were based on items of the BASFI and consisted of seven items representing one domain: physical functioning [12]. The tests were carried out in the following order [11]:

1. *Climbing stairs*: patients faced a flight of 12 steps and were instructed to climb the stairs without using the handrail or a walking aid.
2. *Bending*: patients were instructed to bend forward from the waist and pick up six pens from the floor without an aid and place them on a shelf one by one.
3. *Reaching*: patients faced two shelves placed below each other. Six pens were placed on the lower shelf. Patients were instructed to reach up and place the pens on the highest shelf without help or aids.
4. *Putting on socks*: patients stood barefooted with a pair of socks in one hand and were instructed to put on the socks without help or aids.
5. *Reclining and declining from a chair*: patients were instructed to stand up and sit down three times in a row from the chair without using their hands or any other assistance.
6. *Getting up from the floor*: patients began the test lying supine on the mat and were instructed to get up without help.
7. *Physically demanding activities*: two pylons were placed 10 m apart. Patients were provided with a heart rate monitoring device and were instructed to perform the shuttle walk test. The test was stopped if the patient's heart frequency (HF) exceeded 80% of the HF maximum, if the patient could not keep up with the pace as instructed by the assessor or if the patient wanted to stop.

### *Statistical analyses*

Descriptive statistics were computed by calculating mean and S.D. for all continuous data and percentages for categorical data. Paired samples *t*-tests were used to assess improvement on performance-based tests and self-reported physical functioning (BASFI), disease activity (BASDAI) and spinal and hip mobility (BASMI).

A score for performance-based physical functioning was computed by calculating the mean of the seven performance-based tests [12]. Although the unit of measurement for all tests was the same (i.e., seconds), a standardization procedure was necessary because the distributions between the tests varied (i.e., different mean and S.D.). Therefore raw performance scores were transformed into z-scores. In this way, all tests contributed evenly to the mean performance score.

The ASAS20 response [13, 14] was used to categorize patients as responders or non-responders to anti-TNF therapy. Analogous to the ASAS criteria, an intraindividual improvement of  $\geq 20\%$  was used to classify patients as improvers or non-improvers on performance-based tests of physical functioning. On self-reported physical functioning, patients were defined as improved if they showed an intraindividual improvement of  $\geq 20\%$  and  $\geq 1$  unit on the BASFI. This is the same extent of improvement as described for the BASFI in the ASAS20 improvement criteria [13, 14].

Subsequently, cross-tabulations were produced to establish the concordance between improvers on performance-based physical functioning (number and percentage) in (i) (non-)responders on the ASAS20 criteria and (ii) (non-)improvers on self-reported physical functioning (BASFI). All analyses were performed using SPSS for Windows 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

### *Baseline characteristics*

The study population consisted of 100 patients with a confirmed diagnosis of AS, fulfilling the modified New York criteria. Data for 18 patients were incomplete after follow-up; 7 patients (7%) did not start treatment, 4 stopped treatment within 3 months (4%) and 7 (7%) were not reassessed due to other reasons. No patients were excluded for having pulmonary, cardiovascular or neurological comorbidity affecting the patient's ability to perform daily activities. Accordingly, 82 patients (67.5% men,  $n=56$ ) with a mean age ( $\pm$  S.D.) of 43.9 ( $\pm 11.3$ ) years were reassessed and included in the analyses. Medication at baseline was used by 89% of the study population and consisted mainly of NSAIDs. Table 1 displays the characteristics of the study population.

According to the ASAS20 criteria, 27 (32.9%) patients were categorized as non-responders. After 3 months of anti-TNF therapy, patients experienced a significant decline in self-reported limitations in physical functioning and disease activity, as shown by lower BASFI and BASDAI scores ( $p < 0.0001$ ). Furthermore, an improvement in spinal mobility (BASMI) ( $p < 0.01$ ) and performance-based physical functioning were observed ( $p < 0.0001$ ).

### *Improvement in performance-based tests vs ASAS20 response after anti-TNF therapy*

Table 2 shows the cross-tabulation between (non-)improvers on the performance-based tests and (non-)responders on the ASAS20 response. Improvement in performance-based physical functioning was seen in 70.9% ( $n=39/55$ ) of the responders (i.e.,  $n=39/82 = 47.6\%$  of the

total group). However, 48.1% ( $n=13/27$ ) of the ASAS20 non-responders showed a  $\geq 20\%$  improvement in performance-based physical functioning (i.e.,  $n=13/82 = 15.9\%$  of the total group).

### *Improvement in performance-based vs. self-reported physical functioning after anti-TNF therapy*

The cross-tabulation between (non-)improvers on the performance-based tests and (non-)improvers on self-reported physical functioning (BASFI) is also shown in Table 2. Thirty patients (36.6%) did not improve in physical functioning according to the BASFI after 3 months of anti-TNF therapy. However, 17 of the 30 patients (56.7%) showed an improved performance-based physical functioning (i.e.,  $n=17/82 = 20.7\%$  of the total group).

**Table 1:** Characteristics of 82 AS patients

	Before anti-TNF therapy	After 3 months of anti-TNF therapy	
Men, % ( <i>n</i> )	67.5 (56)		
Age <sup>a</sup> , years	43.9 (11.3)		
Symptom duration <sup>a</sup> , years	21.3 (11.1)		
Disease duration <sup>a</sup> , years	13.4 (9.4)		
Medication, % ( <i>n</i> )			
None	9.6 (8)		
NSAIDs	77.1 (64)		
DMARDs <sup>b</sup>	12.0 (10)		
HLA-B27+, % ( <i>n</i> )	79.5 (66)		
ESR <sup>a</sup> , mm/h	22.8 (19.0)		
Extra-spinal symptoms			
Arthritis, % ( <i>n</i> )	39.8 (33)		
Inflammatory bowel disease, % ( <i>n</i> )	6.0 (5)		
Psoriasis, % ( <i>n</i> )	7.2 (6)		
Uveitis, % ( <i>n</i> )	30.1 (25)		
ASAS20 response, % ( <i>n</i> )			
Responders		67 (55)	
Non-responders		33 (27)	
BASFI <sup>a</sup> , score 0-10	5.4 (2.1)	3.3 (2.4)	$P < 0.0001$
BASDAI <sup>a</sup> , score 0-10	6.0 (1.7)	3.1 (2.1)	$P < 0.0001$
BASMI <sup>a</sup> , score 0-10	4.1 (1.9)	3.7 (1.9)	$P < 0.01$
Performance-based tests <sup>a,c</sup>	1.03 (0.84)	0.72 (0.60)	$P < 0.0001$

<sup>a</sup>Values are presented as mean (S.D.), unless indicated otherwise. <sup>b</sup>DMARDs: SSZ, MTX. <sup>c</sup>Reported score is mean z-score.

**Table 2:** (Non-)improvers (performance-based functioning) vs (non-)responders (ASAS20) and (non-) improvers (self-reported functioning) after 3 months anti-TNF therapy ( $n=82$ )<sup>a</sup>

	Improvement in performance-based physical functioning <sup>b</sup> , $n$ (%)		
	No	Yes	Total
Responder to anti-TNF therapy <sup>c</sup> (ASAS20 response)	<b>No</b> 14 (17.1)	13 (15.9)	27 (32.9)
	<b>Yes</b> 16 (19.5)	39 (47.6)	55 (67.1)
Improvement in self-reported physical functioning <sup>d</sup> (BASFI)	<b>No</b> 13 (15.9)	17 (20.7)	30 (36.6)
	<b>Yes</b> 17 (20.7)	35 (42.7)	52 (63.4)
<b>Total</b>	30 (36.6)	52 (63.4)	82 (100)

<sup>a</sup>Percentages of the total group are given. <sup>b</sup>Improvement defined as  $\geq 20\%$  intraindividual change on performance-based tests. <sup>c</sup>Responder defined according to ASAS20 response criteria: improvement of  $\geq 20\%$  and  $\geq 1$  unit in at least three of four self-reported domains, and no worsening of  $\geq 20\%$  and  $\geq 1$  unit in the remaining domain on an NRS of 0-10. <sup>d</sup>Improvement defined as  $\geq 20\%$  and  $\geq 1$  unit intraindividual change on the BASFI questionnaire.

Of the total group ( $n=82$ ), 57 patients were treated with etanercept and 25 patients were treated with adalimumab. Analyses were repeated and performed separately for etanercept and adalimumab. Analyses yielded similar results to the total group.

## Discussion

This prospective study focused on the improvement in performance-based physical functioning after 3 months of anti-TNF therapy. Our results showed that 48.1% of the AS patients, who were defined as non-responders on the ASAS20 criteria, displayed at least 20% improvement in performance-based physical functioning (i.e., 15.9% of the total group). Furthermore, 56.7% of the patients who did not improve in self-reported physical functioning (BASFI) did improve on the performance-based tests (i.e., 20.7% of the total group).

Until now, outcome after anti-TNF therapy had only been measured with self-reported outcomes like the BASFI, BASDAI 50% response [19] or a combination of self-reported outcomes such as the ASAS20 response (which contains the BASFI). Our results suggest that using both self-reported and performance-based outcome measures could have additional value in evaluating outcome after interventions in AS patients.

We showed that 48.1% of the non-responders to anti-TNF therapy (ASAS20 response) improved in performance-based physical functioning. This suggests that patients improve due to the effects of anti-TNF therapy objectively (e.g., they can get up from the floor more quickly), however, they do not feel better in a subjective way (i.e., they still experience pain,



stiffness and/or fatigue). We also would like to point out that 29.1% ( $n=16/55$ ) of the patients who showed a response according to ASAS criteria did not improve on the performance-based tests. This suggests that patients experience a decline in pain, stiffness or fatigue and/or improvement in self-reported physical functioning after anti-TNF therapy, while the actual level of physical functioning may not have changed at all. Both observations are in line with previous findings that self-reported levels of functioning are strongly related to pain and exertion and less to the time required to complete a task [10, 12]. Also, the contrast between improvement in self-reported (BASFI) and performance-based physical functioning underlines that perceived and actual physical function are two related but distinct entities.

In this study, analogous to the ASAS criteria, a  $\geq 20\%$  intraindividual improvement in performance-based physical functioning was used to categorize patients as improvers or non-improvers. The advantage of this approach is that relative, intraindividual changes may provide a better reflection of clinically meaningful changes for individual patients than absolute changes. In rheumatology, this is a commonly used approach for defining improvement [20]. Also, in the ASAS20 or BASDAI50 criterion [13, 14, 19], an intraindividual change in terms of percentage (i.e., 20% or 50%) for defining improvement after anti-TNF therapy is used.

The question arises as to what extent measurement error can explain changes in performance-based tests. In an earlier publication we showed that the reliability of the performance-based measures is adequate to excellent (ICCs 0.73-0.96) and no systematic differences in the measurements were observed [11]. Therefore, it is unlikely that an intraindividual improvement of 20% or more is only attributable to measurement error.

We propose that evaluating physical functioning is not a matter of choosing one best measurement method. Rather, we would prefer to identify the best combination of measurements that reflects the patients' perspective (i.e., questionnaires) as well as true ability in the physical function domain (i.e., performance-based tests). Using a combination of the BASFI and performance-based tests may provide a better reflection of changes in the physical function domain in AS patients. Patients might be denied continuation of anti-TNF treatment despite their improvement, or they may not be given access to physiotherapy despite limitations in physical functioning.

In conclusion, after 3 months of anti-TNF therapy, improvement in performance-based physical functioning was seen in 48.1% of the ASAS20 non-responders. Performance-based tests provide the opportunity to generate new information in the evaluation of outcome after anti-TNF therapy. In the future, using performance-based tests alongside the BASFI could provide additional value in evaluating outcome for AS patients receiving anti-TNF therapy.

### Key messages

- Performance-based tests of physical functioning showed improvement in 48.1% of the ASAS20 non-responders.
- Evaluation of outcome after anti-TNF therapy in AS is improved by using performance-based tests along with BASFI.

## References

1. Escalas C, Trijau S, Dougados M. Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis. *Rheumatology* 2010, 49: 1317-25.
2. Calin A, Garrett S, Whitelock H, Kennedy LG, O’Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994, 21: 2281-5.
3. Van Tubergen A, Debats I, Ryser L, Londoño J, Burgos-Vargas R, Cardiel MH, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. *Arthritis Rheum* 2002, 47: 242-8.
4. Auleley GR, Benbouazza K, Spoorenberg A, Collantes E, Hajjaj-Hassouni N, van der Heijde D, et al. Evaluation of the smallest detectable difference in outcome or process variables in ankylosing spondylitis. *Arthritis Rheum* 2002, 47: 582-7.
5. Calin A, Nakache JP, Gueguen A, Zeidler H, Mielants H, Dougados M. Outcome variables in ankylosing spondylitis: evaluation of their relevance and discriminant capacity. *J Rheumatol* 1999, 26: 975-9.
6. Ruof J, Stucki G. Comparison of the Dougados Functional Index and the Bath Ankylosing Spondylitis Functional Index. A literature review. *J Rheumatol* 1999, 26: 955-60.
7. Guralnik JM, Branch LG, Cummings SR, Curb JD. Physical performance measures in aging research. *J Gerontol* 1989, 44: M141-6.
8. Hoeymans N, Feskens EJ, van den Bos GA, Kromhout D. Measuring functional status: cross-sectional and longitudinal associations between performance and self-report (Zutphen Elderly Study 1990/1993). *J Clin Epidemiol* 1996, 49: 1103-10.
9. Kivinen P, Sulkava R, Halonen P, Nissinen A. Self-reported and performance-based functional status and associated factors among elderly men: the Finnish cohorts of the Seven Countries Study. *J Clin Epidemiol* 1998, 51: 1243-52.
10. Terwee CB, van der Slikke RM, van Lummel RC, Benink RJ, Meijers WG, de Vet HC. Self-reported physical function was more influenced by pain than performance-based physical function in knee-osteoarthritis patients. *J Clin Epidemiol* 2006, 59: 724-31.
11. van Weely SF, van Denderen CJ, van der Horst-Bruinsma IE, Nurmohamed MT, Dijkmans BA, Dekker J, et al. Reproducibility of performance measures of physical function based on the BASFI, in ankylosing spondylitis. *Rheumatology (Oxford)* 2009, 48(10): 1254-60.
12. van Weely SFE, van Denderen JC, Steultjens MPM, van der Leeden M, Nurmohamed MT, Dekker J, et al. Moving instead of asking? Performance-based tests and BASFI questionnaire measure different aspects of physical function in ankylosing spondylitis. *Arthritis Res Ther* 2012, 14: R52.
13. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001, 44: 1876-86.
14. Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D, ASAS Working Group. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006, 65: 316-20.
15. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the

- New York criteria. *Arthritis Rheum* 1984, 27: 361-8.
16. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994, 21: 2286-91.
  17. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994, 21: 1694-8.
  18. Jones SD, Porter J, Garrett SL, Kennedy LG, Whitelock H, Calin A. A new scoring system for the Bath Ankylosing Spondylitis Metrology Index (BASMI). *J Rheumatol* 1995, 22: 160-9.
  19. Braun J, Pham T, Sieper J, Davis J, van der Linden S, Dougados M, et al., ASAS Working Group. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003, 62: 817-24.
  20. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. *Arthritis Care Res* 2012, 64: 1699-707.