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# Early achievement of ASDAS clinical response is associated with long-term improvements in metrological outcomes in patients with ankylosing spondylitis treated with TNF-α blockers

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**Abstract**

The aim of this study was to investigate the relationship between long-term spinal mobility improvements and early disease activity changes or achievement of clinical response criteria in patients with ankylosing spondylitis (AS) treated with tumor necrosis factor (TNF-α) blockers.

This retrospective study included 112 patients with AS treated with TNF-α blockers for up to 33 months. The paired $t$-test was used to compare outcome measures between visits. The correlation between disease activity changes and metrological improvements was analyzed using cumulative probability plots, Spearman correlation coefficient, and canonical correlation. The difference in metrological outcomes between responders and non-responders to clinical response criteria was also examined.

Metrological and disease activity outcomes improved most markedly in month 3. All disease activity outcomes and ESR from baseline to month 3 (3-month) were significantly correlated with the Bath Ankylosing Spondylitis Metrology Index (BASMI$_{10}$) improvements from baseline to month 33 (33-month). The 3-month changes in ankylosing spondylitis disease activity score (ASDAS-CRP) and patient's global assessment showed a significant correlation with the 33-month changes in chest expansion. Only responders according to ASDAS major improvement at month 3 demonstrated significant 33-month improvements in both BASMI$_{10}$ and chest expansion, compared to non-responders. Responders according to Assessment of Spondylo Arthritis international Society 40 at month 3 showed significant 33-month improvements in BASMI$_{10}$, but not chest expansion, compared to non-responders.

The degree of early changes in disease activity outcomes influenced the extent of long-term metrological improvements in AS treated with TNF-α blockers. Additionally, the achievement of ASDAS- major improvement at month 3 predicted significant metrological improvements throughout long-term TNF-α-blocker therapy.

**Abbreviations:** AS = ankylosing spondylitis, ASAS = Assessment of SpondyloArthritis international Society, ASDAS = ankylosing spondylitis disease activity score, ASDAS-CII = ASDAS clinically important improvement, ASDAS-ID = ASDAS inactive disease, ASDAS-MI = ASDAS major improvement, ASAS20 = at least 20% improvement and 10 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain, ASAS40 = at least 40% improvement and 20 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain, axSpA = axial spondyloarthritis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASDAI50 = at least 50% improvement of BASDAI, compared with baseline, BASMI = bath ankylosing spondylitis metrology index, MRI = magnetic resonance imaging, PhGA = physician's global assessment, PtGA = patient's global assessment, TNF = tumor necrosis factor.

**Keywords:** ankylosing spondylitis, tumor necrosis factor blocker, bath ankylosing spondylitis metrology index, chest expansion, ankylosing spondylitis disease activity score major improvement

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# 1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory axial spondyloarthritis (axSpA) characterized by the predominant involvement of the sacroiliac joints and spine and is accompanied by characteristic inflammatory back pain, followed by functional impairment and structural damage, which lead to a decreased health-related quality of life, especially, in active, productive, and resilient young adults.[1] Recently, the Assessment of SpondyloArthritis international Society (ASAS)-European League Against Rheumatism (EULAR) updated the management recommendation for axSpA and emphasized the maximization of long-term health-related quality of life as the primary goal of treating the patients with axSpA through a combination of non-pharmacological and pharmacological treatment modalities.[2]

Tumor necrosis factor (TNF)-α blockers have proven to be highly efficacious pharmacological therapy for patients with AS who do not respond to conventional treatment, contributing to a notable improvement in disease activity, spinal inflammation demonstrated by magnetic resonance imaging (MRI), functional outcome, and quality of life.[3–12] Radiographic spinal progression may be impeded after long-term TNF-α-blocker therapy, although there is some debate regarding this.[13–16] Concerning spinal mobility, most studies demonstrated that it significantly improved after short-term therapy[4–6] and maintained a favorable condition after a significant improvement, despite some progression in spinal structural damage.[17–19] However, studies of the factors associated with spinal mobility improvement throughout long-term TNF-α-blocker therapy are rare.[19]

Spinal mobility is usually measured with the Bath AS Metrology Index (BASMI), which was developed to measure the status of the axial skeleton accurately and to objectively assess clinically significant changes in spinal function in AS patients and is the most reliable and clinically useful metrological measurement.[20,21] However, because thoraco-abdominal movement shows a poor relationship with BASMI,[22] the use of chest expansion in conjunction with BASMI is recommended for a more accurate assessment of thoracic spinal mobility.[21,23] Spinal mobility is determined by radiographic spinal progression and spinal inflammation,[24] both of which are closely related to disease activity outcomes, such as Bath AS Disease Activity Index (BASDAI) and the AS Disease Activity Score (ASDAS), and acute phase reactants (ESR and CRP).[10,11,15,19,25–29] Radiographic spinal progression was noted to be longitudinally associated with disease activity outcomes and inflammatory markers in patients with AS treated with[15,19] and without[26] TNF-α-blockers. Inflammation in the sacroiliac joint or spine measured with MRI showed a longitudinal relationship with ASDAS, but not BASDAI,[10,11,29] which may be because ASDAS has demonstrably better psychometric properties than patient-reported outcomes through the incorporation of CRP with patient-reported outcomes.[21,30,31]

However, the direct relationship between long-term spinal mobility improvements and early disease activity outcome changes during TNF-α-blocker therapy has not been precisely defined. Furthermore, there is no documentation whether achievement of clinical response criteria, including BASDAI, ASDAS, and ASAS response criteria, influences long-term spinal mobility improvements in AS patients treated with TNF-α blockers. In this study, we investigated the relationship between long-term spinal mobility improvements and early disease activity changes or achievement of clinical response criteria in AS patients treated with TNF-α blockers.

# 2. Methods

## 2.1. Patients

We performed a single center retrospective review of 112 patients with AS who were treated with TNF-α blockers for up to 33 months between January 2006 and December 2014. All patients were more than 19 years old, fulfilled the 1984 modified New York criteria for AS,[32] and started TNF-α-blocker therapy according to the Korean National Health Insurance guideline, which recommends that TNF-α blockers may be used in patients who have active disease with BASDAI $\geq$ 40/100, despite concurrent treatment with 2 or more anti-rheumatic drugs, including NSAIDs, for at least 3 months. The Ethics Committee of the Kyungpook National University Hospital approved this study (KNUH 2018-06-028).

## 2.2. Clinical and Demographic Data

Patients were evaluated at baseline, after 3 months, and then every 6 months for up to 33 months. Spine and hip mobility were assessed with $BASMI_{10}$, $BASMI_{10}$ components, and chest expansion. Disease activity was measured by ASDAS based on CRP (ASDAS-CRP), BASDAI, patient's global assessment (PtGA), physician's global assessment (PhGA), spinal pain, and acute phase reactants (ESR and CRP). Physical functionality was determined by the Bath AS Functional Index. Clinical efficacy was presented using the ASDAS response criteria,[33] ASAS response criteria,[34] and at least 50% improvement of BASDAI, compared with baseline (BASDAI50). ASDAS response criteria include ASDAS major improvement (ASDAS-MI, a change of $\geq$ 2.0 units, compared with baseline), ASDAS clinically important improvement (ASDAS-CII, a change of $\geq$ 1.1 units, compared with baseline), and ASDAS inactive disease (ASDAS-ID, ASDAS < 1.3). The ASAS response criteria include at least 20% improvement and 10 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain (ASAS20) and at least 40% improvement and 20 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain (ASAS40). At 3 months and every 6 months afterward, the continuation of TNF-α-blocker therapy was determined based on BASDAI improvement (BASDAI50 or absolute improvement of $\geq$ 2 units compared with baseline), which was used as the definition of treatment response in this study. Patients who showed resistance or side effects to a TNF-α blocker were allowed to change to a different 1.

## 2.3. Statistical Analysis

Descriptive statistics are expressed as mean ± standard deviation (S.D) or mean ± standard error (S.E). Continuous variables were compared using Student $t$-test or 1 way analysis of variance analysis. Categorial variables were compared between the groups using the chi-square test or Fisher exact test. For analysis of drug survival, we used Kaplan-Meier analysis with log-rank test comparing patients with three different TNF-α blockers. The paired t-test was used to compare outcome measures between visits. The combined scatter and cumulative probability plots, in which the individual changes in $BASMI_{10}$ and chest expansion from baseline to month 33 (33-month) were shown in cumulative order versus the 3-month changes in disease activity outcomes,

were used to demonstrate an association between metrological improvements and disease activity outcome changes. Correlation coefficients between the 33-month improvements in metrological outcomes and the 3-month changes in disease activity outcomes were demonstrated using the Spearman correlation coefficient. As multiple time points were measured in this study, canonical correlation analysis was used to identify the linear combination of time points that maximizes the correlation between the changes in disease activity outcomes from baseline to month 3 (3-month) and improvements in metrological outcomes over 33 months. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Kaplan-Meier product-limit estimates plot was drawn R ver 3.6.0 platform with 'rms' package. All statistical testing was performed at the $\alpha = 0.05$ significance level of both sides.

## 3. Results

### 3.1. Demographic findings and baseline characteristics

Table 1 shows the baseline demographic and clinical character-istics of patients with AS. The mean patient age was $38.2 \pm 11.8$ years. Most patients were male (89.3%) and had the HLA-B27 antigen (97.7%). Among the patients, 30.4% had a history of anterior uveitis. All patients demonstrated high or very high disease activity,[26,33] with a mean baseline ASDAS-CRP of $3.8 \pm 0.8$, BASDAI of $5.8 \pm 1.2$, PtGA of $6.6 \pm 1.7$, PhGA of $6.5 \pm 1.6$, and spinal pain of $6.5 \pm 1.7$. The mean baseline $BASMI_{10}$ and chest expansion were $4.3 \pm 2.4$ and $2.6 \pm 1.3$, respectively. Syndesmophyte was detected in 56 of 112 patients (50.0%). Among the 112 patients, etanercept, adalimumab, and infliximab were used in 50 (44.6%), 52 (46.4%), and 10 (8.9%) patients, respectively. Overall, twenty-five patients (22.3%) discontinued TNF-α-blocker therapy: 10 for etanercept, 13 for adalimumab,

and 2 for infliximab. The drug survival was not different among the 3 TNF-α blockers ($P = .786$) (Supplemental Digital Content (Figure S1, http://links.lww.com/MD/E996)). The reasons for discontinuation were adverse events (36%, n=9), inefficacy (4%, n=1), lost to follow-up due to residence movement (28%, n=7), and intension of patients (32%, n=8). Malignancies and infection were not reported. Adverse events to discontinuation included recurrent uveitis (4%, 1 patient taking etanercept), injection site response (12%, n=3), and systemic side effects (20%, n=5), including fever, myalgia, urticaria, and vasculitic skin lesion. Inefficiency to discontinuation was observed in 1 patient taking adalimumab after 3 months of treatment and this patient did not want to use a second TNF-α blocker. On the other hand, we included 5 patients who switched to a second TNF-α blocker after discontinuing their first drug due to inefficacy; 3 for infliximab and 2 for adalimumab. All these 5 patients continued their second TNF-α-blocker therapy up to 33 months without cross-resistance.

### 3.2. Relationship between improvements in metrological outcomes and changes in disease activity outcomes

TNF-α blockers demonstrated a notable therapeutic effect on metrological outcomes during the first 3 months (Table 2). $BASMI_{10}$ showed rapid and significant improvements to month 3 ($4.3 \pm 2.3$ vs $3.5 \pm 2.3$, $P < .001$) and further responses to month 9 ($3.5 \pm 2.3$ vs $3.3 \pm 2.4$, $P = .003$), and then maintained until month 33. For $BASMI_{10}$ components, all components improved markedly to month 3 and components of anterior lumbar flexion, lumbar side flexion, and intermalleolar distance demonstrated further significant improvements to month 9. The improvements in the $BASMI_{10}$ components also sustained until month 33. Chest expansion increased considerably from $2.6 \pm 1.3$ at baseline to $2.9 \pm 1.3$ at month 3 ($P = .026$) and then remained stable up to month 33. Three TNF-α blockers showed similar 33-month improvements in $BASMI_{10}$ and chest expansion (Supplemental Digital Content (Table S1, http://links.lww.com/MD/E998)).

All disease activity outcomes and acute phase reactants improved most significantly by month 3. Among the disease activity outcomes, ASDAS-CRP changed significantly by month 3 ($3.8 \pm 0.8$ vs $1.7 \pm 0.6$, $P < .001$) and by month 9 ($1.7 \pm 0.6$ vs $1.5 \pm 0.5$, $P < .001$), maintained until month 27, and then showed non-marked but significant improvements by month 33 ($1.4 \pm 0.6$ vs $1.3 \pm 0.6$, $P = .027$). BASDAI showed significant and continued improvements up to month 33. Other disease activity outcomes, including PtGA, PhGA, and spinal pain, significantly improved up to month 27 and then maintained to month 33.

We evaluated the relationship between the 3-month changes in disease activity outcomes and the 33-month metrological improvements. First, we used cumulative probability plots, in which scatter plots of the individual 3-month differences in disease activity outcomes aggregate order versus the 33-month $BASMI_{10}$ (Fig. 1A, C, E, G, I) or chest expansion improvements were employed (Fig. 1B, D, F, H, J). The 33-month $BASMI_{10}$ improvements tended to increase with respect to each of the 3-month changes in disease activity outcomes, while the 33-month chest expansion improvements did not demonstrate remarkable changes toward the 3-month changes in disease activity outcomes. Next, the association at the group level was assessed using the Spearman correlation coefficients (Table 3). Each of the 3-month changes in disease activity outcomes and ESR was significantly correlated with the 33-month $BASMI_{10}$ improve-

## Table 1

**Baseline demographic and clinical characteristics of the patients with ankylosing spondylitis (AS).**

| Characteristics | Results |
| --- | --- |
| Patient (male, %) | 112 (100, 89.3) |
| Age, yr | 38.2 ± 11.8 |
| HLA-B27 positive | 88/90 (97.7) |
| Uveitis | 34/112 (30.4) |
| ASDAS-CRP | 3.8 ± 0.8 |
| BASDAI (0-10) | 5.8 ± 1.2 |
| PtGA (0-10) | 6.6 ± 1.7 |
| PhGA (0-10) | 6.5 ± 1.6 |
| Spinal pain (0-10) | 6.5 ± 1.7 |
| BASFI (0-10) | 4.5 ± 2.2 |
| $BASMI_{10}$ | 4.3 ± 2.4 |
| Chest expansion | 2.6 ± 1.3 |
| ESR (mm/hr) | 33.4 ± 25.0 |
| CRP (mg/dL) | 2.4 ± 2.5 |
| Syndesmophyte (≥ 1) | 56/112 (50.0) |
| Used drugs | |
| Etanercept | 50 (44.6) |
| Adalimumab | 52 (46.4) |
| Infliximab | 10 (8.9) |

Values are presented as number of patients (%) or mean ± standard deviation (S.D). HLA, human leukocyte antigen; ASDAS-CRP, ankylosing spondylitis disease activity score based on CRP; BASDAI, Bath ankylosing spondylitis disease activity index; PtGA, patient's global assessment; PhGA, physician's global assessment; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis metrology index.

**Table 2**

Improvements in disease activity and metrological outcomes over 33 months with TNF-α-blocker treatment in patients with ankylosing spondylitis.

| Out come measure | Base line (n=112) | Month 3 (n=110) | P | Month 9 (n=106) | P | Month 15 (n=102) | P | Month 21 (n=96) | P | Month 27 (n=95) | P | Month 33 (n=87) | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BASMI$_{10}$ | 4.3±2.3 | 3.5±2.3 | <.001 | 3.3±2.4 | .001 | 3.3±2.3 | NS | 3.2±2.5 | NS | 3.2±2.4 | NS | 3.3±2.4 | NS |
| Tragus-to-wall distance | 15.8±7.0 | 14.8±6.8 | <.001 | 14.6±6.7 | NS | 14.6±6.5 | NS | 14.8±6.6 | NS | 14.9±6.9 | NS | 15.2±7.0 | NS |
| Lumbar flexion | 3.1±2.3 | 3.6±2.4 | <.001 | 3.8±2.4 | .015 | 3.9±2.3 | NS | 3.9±2.5 | NS | 3.8±2.3 | NS | 3.8±2.3 | NS |
| Inter-malleolar distance | 93.0±24.7 | 100.6±20.0 | <.001 | 103.3±19.4 | .025 | 104.6±20.5 | NS | 105.9±22.0 | NS | 106.7±21.1 | NS | 109.2±22.6 | .003 |
| Cervical rotation | 48.8±25.6 | 58.1±26.3 | <.001 | 59.0±27.9 | NS | 59.5±28.1 | NS | 61.0±28.8 | NS | 61.7±28.2 | NS | 61.2±28.8 | NS |
| Lumbar side flexion | 10.0±6.9 | 12.7±7.8 | <.001 | 13.5±8.0 | .006 | 13.9±8.0 | NS | 14.0±8.3 | NS | 14.0±8.2 | NS | 13.7±8.2 | NS |
| Chest expansion | 2.6±1.3 | 2.9±1.3 | .026 | 3.2±1.6 | NS | 3.3±1.6 | NS | 3.5±1.6 | NS | 3.4±1.4 | NS | 3.4±1.2 | NS |
| ASDAS-CRP | 3.8±0.8 | 1.7±0.6 | <.001 | 1.5±0.5 | <.001 | 1.4±0.6 | NS | 1.4±0.6 | NS | 1.4±0.6 | NS | 1.3±0.6 | .027 |
| BASDAI | 5.8±1.2 | 2.4±1.2 | <.001 | 1.7±0.9 | <.001 | 1.5±0.9 | <.001 | 1.3±1.0 | .037 | 1.2±0.9 | .025 | 1.1±0.8 | .038 |
| PtGA | 6.6±1.7 | 3.5±2.0 | <.001 | 2.9±1.9 | <.001 | 2.5±1.8 | <.001 | 2.3±1.8 | .010 | 2.0±1.6 | .015 | 2.0±1.6 | NS |
| PhGA | 6.5±1.6 | 3.4±1.9 | <.001 | 2.8±1.8 | <.001 | 2.4±1.7 | <.001 | 2.1±1.7 | .001 | 1.8±1.5 | .001 | 1.7±1.5 | NS |
| Spinal pain | 6.5±1.7 | 2.8±1.9 | <.001 | 2.1±1.5 | <.001 | 1.9±1.5 | .017 | 1.8±1.6 | .039 | 1.5±1.4 | .002 | 1.5±1.4 | NS |
| ESR, mm/hour | 33.9±25.1 | 8.6±12.5 | <.001 | 8.5±10.0 | NS | 9.8±12.6 | .017 | 10.8±12.7 | NS | 12.2±11.9 | .040 | 11.5±13.8 | NS |
| CRP, mg/dl | 2.5±2.5 | 0.3±0.8 | <.001 | 0.2±0.4 | NS | 0.3±0.7 | .040 | 0.4±0.9 | NS | 0.4±0.8 | NS | 0.4±0.8 | NS |

The P values represent differences in data between visits using the paired t-test. ASDAS-CRP = ankylosing spondylitis disease activity score based on CRP; BASDAI = bath ankylosing spondylitis disease activity index; BASMI = bath ankylosing spondylitis metrology index, PtGA = patient's global assessment; PhGA = physician's global assessment; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NS = non-specific.

ments (ASDAS-CRP, $r=0.298$, $P=.009$; BASDAI, $r=0.397$, $P<.001$; PtGA, $r=0.268$, $P=.017$; PhGA, $r=0.262$, $P=.020$; spinal pain, $r=0.278$, $P=.013$; ESR, $r=0.273$, $P=.015$; CRP, $r=0.216$, $P=.056$). For chest expansion, only the 3-month changes in ASDAS-CRP ($r=-0.249$, $P=.030$) and PtGA ($r=-0.293$, $P=.009$) showed a significant correlation with the 33-month chest expansion improvements. Taken together, the 3-month changes in ASDAS-CRP and PtGA influenced both of the long-term BASMI$_{10}$ and chest expansion improvements in patients with AS treated with TNF-α blockers.

Additionally, we assessed the strength of global correlation of metrological outcomes over 33 months according to 3-month changes in disease activity outcomes using canonical correlation analysis (Supplemental Digital Content (Table S2, http://links.lww.com/MD/E999)). The 3-month changes in ASDAS-CRP, BASDAI, PhGA, and spinal pain showed a significant global relationship with BASMI$_{10}$ improvements over 33 months (ASDAS-CRP, $r=0.456$, $P=.028$; BASDAI, $r=0.478$, $P=.012$; PhGA, $r=0.479$, $P=.012$; spinal pain, $r=0.496$, $P=.007$), while the 3-month changes in ESR, CRP, and PtGA were not significantly associated with them. Only the 3-month changes in PhGA were significantly correlated with global chest expansion improvements over 33 months ($r=-0.455$, $P=.040$).

### 3.3. Relationship between improvements in metrological outcome and achievement of clinical response criteria

To appropriately assess the clinical efficacy of TNF-α blockers, we determined the ASAS, ASDAS, and BASDAI clinical response criteria at each time point. TNF-α-blocker therapy demonstrated a considerable achievement of the ASDAS response criteria, including ASDAS-MI, ASDAS-CII, and ASDAS-ID (Fig. 2). The response rates of ASDAS-MI were 56.0, 66.3, 61.3, 70.5, 71.3, and 75.0% at months 3, 9, 15, 21, 27, and 33, respectively. The percentages of ASDAS-CII and ASDAS-ID responders ranged from 90.0 to 95.9% and from 26.4 to 64.4%, respectively. In the case of the ASAS response criteria, the ASAS40 responder percentages were 52.9, 66.7, 71.9, 72.2, 80.9, and 84.0% at months 3, 9, 15, 21, 27, and 33, respectively. The ASAS20 response rates ranged from 84.3 to 91.4%. The BASDAI50

response rates ranged from 75.5 to 98.9% during the treatment period. Three TNF-α blockers showed similar clinical efficacies according to ASDAS, ASAS, and BASDAI clinical response criteria (Supplemental Digital Content (Figure S2, http://links.lww.com/MD/E997)).

As the 3-month changes in disease activity outcomes showed a close relationship with long-term spinal mobility improvements, we investigated whether achievement of the clinical response criteria at month 3 was associated with the 33-moth metrological improvements (Fig. 3 and Supplemental Digital Content (Table S3, http://links.lww.com/MD/E1000)). Baseline BASMI$_{10}$ and chest expansion did not differ between responders and non-responders when subgroups were defined according to any clinical response criteria. With regard to ASDAS response criteria, responders according to the ASDAS-MI at month 3 demonstrated significant 33-month improvements in both BASMI$_{10}$ and chest expansion, compared to non-responders (BASMI$_{10}$, -1.3±0.2 vs -0.7±0.2, $P=.025$; chest expansion, 1.0 ±0.2 vs 0.4±0.2, $P=.018$). In contrast, achievement of the ASDAS-CII or ASDAS-ID at month 3 did not show a significant differences in the 33-month metrological improvements (ASDAS-CII: BASMI$_{10}$, $P=.237$; chest expansion, $P=.816$; ASDAS-ID: BASMI$_{10}$, $P=.539$; chest expansion, $P=.489$).

About ASAS response criteria, responders according to the ASAS40 at month 3 showed significantly higher improvements in the 33-month BASMI$_{10}$ (-1.3±0.2 vs -0.7±0.2, $P=.020$), but not chest expansion (0.9±0.2 vs 0.5±0.2, $P=.085$), compared to non-responders. Achievement of the ASAS20 response criteria at month 3 did not demonstrate any significant differences in the 33-month improvements in BASMI$_{10}$ ($P=.189$) or chest expansion ($P=.650$). Additionally, achievement of the BAS-DAI50 at month 3 did not demonstrate any significant differences in the 33-month improvements in BASMI$_{10}$ ($P=.070$) or chest expansion ($P=.511$).

## 4. Discussion

Spinal mobility is a core component of the evaluation of clinical practice and trials in AS,[19,23,24] and shows sustained improvements or stable status after initial improvements throughout
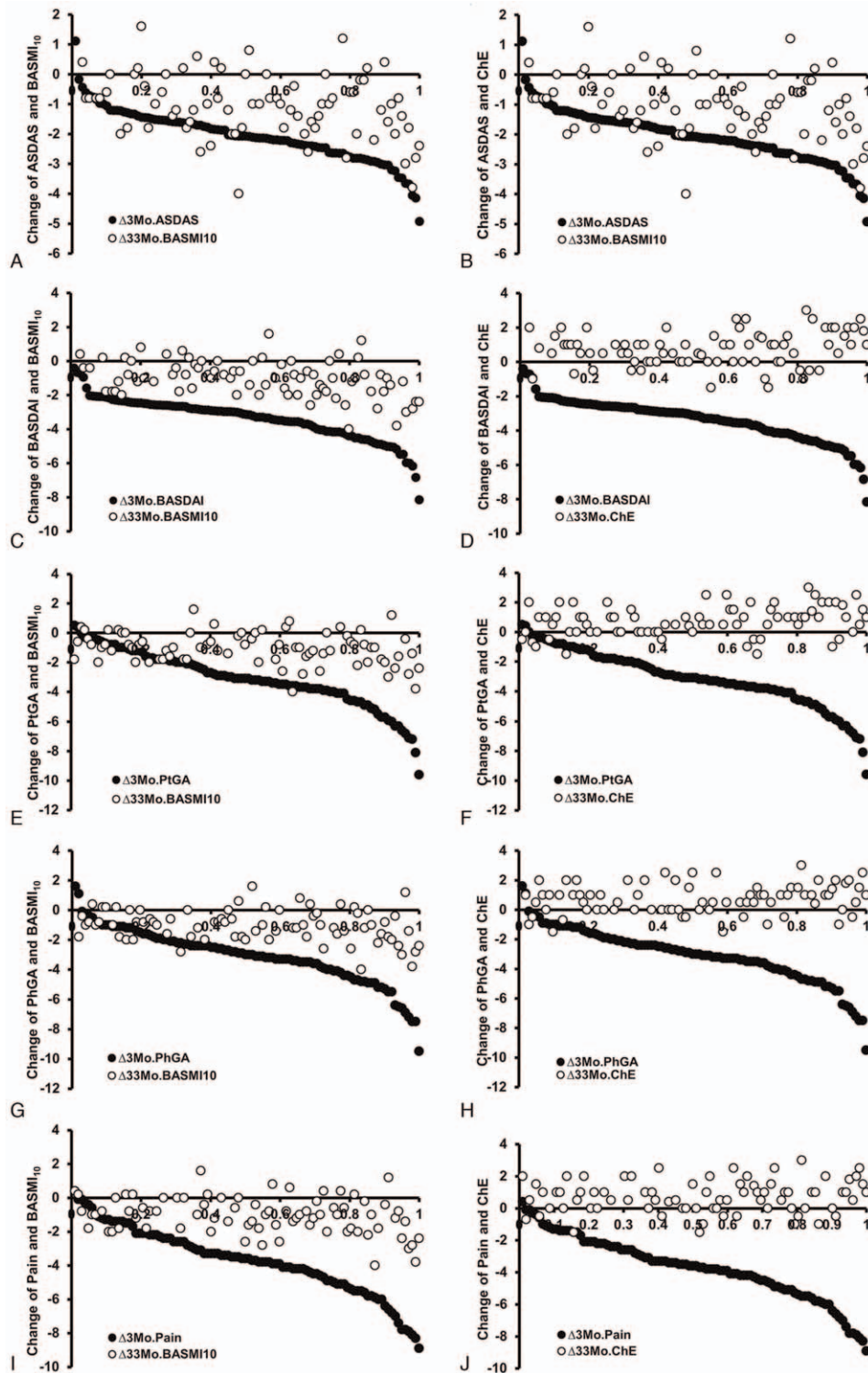
**Figure 1.** Cumulative probability plots of improvements in BASMI$_{10}$ and chest expansion from baseline to month 33 (33-month) in relation to changes in disease activity outcomes from baseline to month 3 (3-month). The 33-month BASMI$_{10}$ improvements are demonstrated in relation to 3-month changes in (A) ASDAS-CRP, (C) BASDAI, (E) patient's global assessment, (G) physician's global assessment, and (I) spinal pain. The 33-month chest expansion improvements are shown in 3-month changes in (B) ASDAS-CRP, (D) BASDAI, (F) patient's global assessment, (H) physician's global assessment, and (J) spinal pain. Δ3Mo.ASDAS, ASDAS-CRP changes from baseline to month 3; Δ3Mo.BASDAI, BASDAI changes from baseline to month 3; Δ3Mo.PtGA, changes in patient's global assessment from baseline to month 3; Δ3Mo.PhGA, changes in physician's global assessment from baseline to month 3; Δ3Mo.pain, spinal pain changes from baseline to month 3; Δ33Mo.BASMI$_{10}$, BASMI$_{10}$ improvements from baseline to month 33; Δ33Mo.ChE, chest expansion improvements from baseline to month 33.

Correlation between changes in disease activity outcomes at month 3 and metrological outcome improvements at month 33[a].

| | $\Delta$33Mo.BASMI$_{10}$ | P | $\Delta$33Mo.Chest expansion | P |
|---|---|---|---|---|
| $\Delta$3Mo.ASDAS-CRP | 0.298 | .009 | −0.249 | .030 |
| $\Delta$3Mo.BASDAI | 0.397 | <.001 | −0.213 | .056 |
| $\Delta$3Mo.PtGA | 0.268 | .017 | −0.293 | .009 |
| $\Delta$3Mo.PhGA | 0.262 | .020 | −0.191 | .094 |
| $\Delta$3Mo.Pain | 0.278 | .013 | −0.118 | .304 |
| $\Delta$3Mo.ESR | 0.273 | .015 | −0.142 | .211 |
| $\Delta$3Mo.CRP | 0.216 | .056 | −0.112 | .327 |

ASDAS-CRP = ankylosing spondylitis disease activity score based on CRP; BASDAI = bath ankylosing spondylitis disease activity index, PtGA = patient's global assessment; PhGA = physician's global assessment.

[a] Spearman correlation coefficient was used to demonstrate the correlation between the 3-month changes in disease activity outcomes and the 33-month improvements in metrological outcomes. $\Delta$33Mo.BASMI$_{10}$, BASMI$_{10}$ improvement from baseline to month 33; $\Delta$33Mo.Chest expansion, chest expansion improvement from baseline to month 33; $\Delta$3Mo.BASDAI, BASDAI change from baseline to month 3; $\Delta$3Mo.PtGA, change in patient's global assessment from baseline to month 3; $\Delta$3Mo.PhGA, change in physician's global assessment from baseline to month 3; $\Delta$3Mo.Pain, spinal pain change from baseline to month 3; $\Delta$3Mo.ASDAS-CRP, ASDAS-CRP change from baseline to month 3.

long-term TNF-α-blocker therapy.[19,35] In this study, we focused on the factors that may determine the long-term spinal mobility improvements in AS patients during TNF-α-blocker therapy. As in previous studies,[18,19,35] we found that TNF-α blockers exhibited long-term effects on BASMI$_{10}$, BASMI$_{10}$ components, and chest expansion, with rapid improvement after only 3-months of treatment. Long-term improvements in BASMI$_{10}$, but not chest expansion, were significantly associated with early disease activity changes and the achievement of ASDAS-MI response criteria at month 3 was associated with long-term improvements in both BASMI$_{10}$ and chest expansion.

Our results of the close relationship between the 3-month changes in disease activity outcomes, especially ASDAS-CRP, and the 33-month metrological improvements are supported by previous studies of the association between spinal MRI inflammation or spinal progression, both of which contribute to the impairment of spinal mobility,[24] and disease activity outcomes.[10,15,26–28] Improvements in spinal MRI inflammation were detected early TNF-α-blocker therapy,[10,27] and were correlated with early decrease in BASDAI[27] and ASDAS.[10] Radiographic spinal progression, assessed by the modified Stoke AS Spine Score, was also contributed by ASDAS and BASDAI in advanced AS patients who were naïve to TNF-α blockers.[26] TNF-α blockers have been demonstrated to reduce radiographic progression in patients with AS in prospective[12,13] and retrospective[14] studies and showed an indirect effect on spinal progression via a reduction in ASDAS in the Swiss Clinical Quality Management cohort study.[15] Therefore, early significant improvements in disease activity outcomes with TNF-α-blocker therapy are related to the rapid resolution of inflammatory spinal lesions and the efficient suppression of spinal progression, which leads to early significant and subsequent stabilization of metrological improvements.

Chest expansion is the only measure available for monitoring thoracic involvement, and the ASAS group recommends the addition of chest expansion to the core set for the clinical evaluation of AS patients.[21] Some randomized controlled trials with TNF-α blockers in AS demonstrated that a few months of treatment induced chest expansion improvement, compared to a placebo group.[5,6] We demonstrated that chest expansion improved significantly after 3-months of treatment and then maintained the attained favorable condition over time, but the relationship between chest expansion improvements and changes in disease activity outcomes was unclear. There is some disagreement over whether chest expansion improves after TNF-α-blocker therapy in AS[4,5,6] because chest expansion has disadvantages such as significant inter-tester variability, poor reproducibility, high dependence on patient effort, and a broad range of normal values with an age-related decrease.[22,36] Therefore, it is necessary to clarify whether chest expansion can efficiently assess spinal mobility change with TNF-α-blocker therapy in AS patients.

Among the clinical response criteria, ASAS20 and ASAS40 have been used as primary endpoints in clinical trials with AS[4,5,6] and non-radiographic axSpA,[17,37] respectively, and
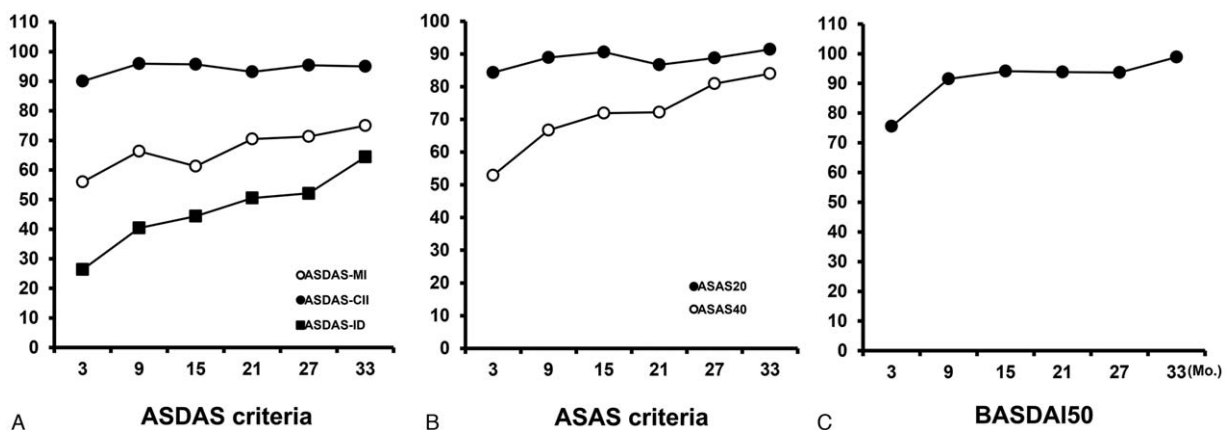
**Figure 2.** Response to TNF-α-blocker therapy, as measured by (A) ASDAS response criteria, (B) ASAS response criteria, and (C) BASDAI response criteria over 33 months. ASDAS criteria, response criteria of ankylosing spondylitis disease activity score; ASDAS-MI, ASDAS major improvement; ASDA-CII, ASDAS clinically important improvement; ASDAS-ID, ASDAS inactive disease; ASAS criteria, Assessment of SpondyloArthritis international Society criteria; ASAS20, at least 20% improvement and 10 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain; ASAS40, at least 40% improvement and 20 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain. BASDAI50, an improvement of ≥ 50% of BASDAI, compared with baseline.
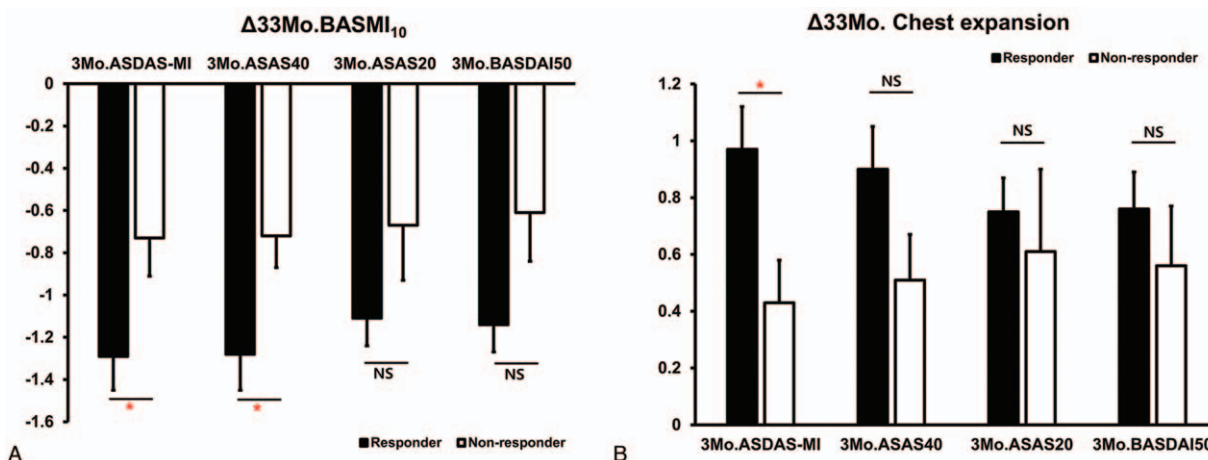
**Figure 3.** Metrological improvements from baseline to month 33 (33-month) according to clinical response criteria at month 3 in AS patients treated with TNF-$\alpha$ blockers. (A) $BASMI_{10}$ and (B) chest expansion. $\Delta$33Mo. $BASMI_{10}$, $BASMI_{10}$ improvement from baseline to month 33; $\Delta$33Mo.Chest expansion, chest expansion improvement from baseline to month 33; 3Mo.ASDAS-MI, responsiveness according to ASDAS major improvement at month 3; 3Mo.ASAS20, responsiveness according to at least 20% improvement and 10 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain at month 3; 3Mo.ASAS40, responsiveness according to at least 40% improvement and 20 units of absolute change in 3 of 4 domains, using the same domains as the ASAS response criteria, without any worsening in the fourth domain at month 3; 3Mo. BASDAI50, responsiveness according to an improvement of $\geq$ 50% of BASDAI, compared with baseline, at month 3. NS, non-specific. Values are mean$\pm$S.E. $^{*}P < .05$.

ASDAS was used to assess clinical efficacy in clinical trials of SpA.[2] ASAS40 is a stricter criterion than ASAS20,[38] but a less stringent criterion than ASDAS-MI.[33] ASDAS includes both symptoms related to AS and assessments made by physicians, including CRP or ESR, and is highly discriminatory for differentiating patients with different levels of change, which is imperative in assessing treatment efficacy in clinical trials.[30,31] ASDAS-CII identified more patients with clinically meaningful improvements, compared to BASDAI50 or ASAS20,[33] and ASDAS-MI showed a higher capacity for discriminating between active and placebo groups, compared to usual response criteria.[10,33] Previous studies of the relationship between MRI inflammation and clinical response criteria showed that the ASDAS response criteria (ASDAS-CII) better reflected spinal inflammatory changes than other composite measures in AS,[11] whereas the achievement of ASAS20 response criteria was not significantly associated with MRI inflammatory changes in AS patients treated with golimumab.[10] In our study, only responders to the ASDAS-MI exhibited the 33-month improvements in both $BASMI_{10}$ and chest expansion, compared to non-responders. Responders to the ASAS40 response criteria at month 3 demonstrated better improvements in the 33-month $BASMI_{10}$, but not chest expansion, compared to non-responders. These results suggest that a more substantial change in disease activity outcomes at the early phase of treatment reflects a higher spinal inflammatory change at the same time and is related to better long-term improvement in metrological outcomes in AS with TNF-$\alpha$-blocker therapy.

Our study had some noteworthy limitations. First, because variable degrees of syndesmophytes were detected in 55.8% of the patients, syndesmophytes may have influenced the outcome of spinal mobility, despite the resolution of inflammation during TNF-$\alpha$-blocker treatment. Second, because we did not use radiologic measures such as the modified Stoke AS Spine Score scoring system for the quantification of spinal progression, we could not analyze the effect of long-term TNF-$\alpha$-blocker therapy

on radiographic progression and the correlation between spinal progression and $BASMI_{10}$ changes.

In conclusion, our study showed that long-term metrological improvements during TNF-$\alpha$-blocker therapy were significantly related to early changes in disease activity outcomes and that the achievement of ASDAS-MI response criteria at month 3 may be a valuable predictive factor of long-term improvements in metrological outcomes. Further studies seem to be required to determine whether achievement of ASDAS-MI at month 3 is a good predictor of suppression of radiologic progression along with metrological improvements during TNF-$\alpha$-blocker therapy in AS.

## Author contributions

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**Data curation:** Eon Jeong Nam
**Formal analysis:** Won Kee Lee
**Methodology:** Eon Jeong Nam
**Supervision:** Eon Jeong Nam
**Writing & editing:** Eon Jeong Nam

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