The Clinical Meaning of Walking Speed as Measured by the Timed 25-Foot Walk in Patients With Multiple Sclerosis

Jeffrey A. Cohen, MD; Arun V. Krishnan, PhD; Andrew D. Goodman, MD; James Potts, PhD; Ping Wang, PhD; Eva Havrdova, MD; Chris Polman, MD; Richard A. Rudick, MD

IMPORTANCE Walking impairment, a common clinical manifestation of multiple sclerosis (MS), is often measured in clinical practice and clinical trials using the Timed 25-Foot Walk (T25-FW).

OBJECTIVE To evaluate the relationship between walking speed measured by the T25-FW and the Physical Component Summary (PCS) score of the 36-Item Short Form Health Survey (SF-36) to better understand the clinical meaning of T25-FW walking speed in MS.

DESIGN, SETTING, AND PARTICIPANTS We retrospectively analyzed data from 3 clinical trials (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis [AFFIRM], Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing-Remitting Multiple Sclerosis [SENTINEL], and International MS Secondary Progressive Avonex Controlled Trial [IMPACT]) that included T25-FW and SF-36 scores as outcomes in patients with MS. Patients had secondary-progressive MS and an Expanded Disability Status Scale score of 3.5 to 6.5 or relapsing-remitting MS and an Expanded Disability Status Scale score of 0 to 5.0.

MAIN OUTCOMES AND MEASURES We used Spearman rank correlation and Pearson product moment correlation (r) and descriptive statistics to evaluate retrospectively the relationship between the SF-36 PCS score and T25-FW walking speed at baseline and the 2-year changes from baseline.

RESULTS Among all 2549 patients from the 3 trials, walking speed and SF-36 PCS score at baseline were significantly correlated (n = 2333; r = 0.48; P < .001). In placebo-treated patients at 2 years, the percentage of change from baseline in walking speed was significantly correlated with the change from baseline in SF-36 PCS score (r = 0.35; P < .001). Significant correlations between the change in SF-36 PCS scores and the percentage of change in walking speed at 2 years also were observed in groups receiving active treatment (r, 0.13-0.28; P ≤ .005). Among placebo-treated patients, 27.5% had a clinically meaningful worsening (≥5-point decrease) in SF-36 PCS scores during the 2 years. Walking speed declined by 21.8% in these patients after 2 years, but only by 5.4% in those without worsening of SF-36 PCS scores.

CONCLUSIONS AND RELEVANCE In patients with MS, walking speed measured using the T25-FW correlated with SF-36 PCS scores such that a decline in walking speed of 20% to 25% corresponded to a clinically meaningful worsening of SF-36 PCS scores. A 20% to 25% decline in walking speed may be a clinically meaningful threshold for defining worsening using the T25-FW in MS clinical trials and for monitoring patients in clinical settings.
Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that often leads to accumulation of irreversible disability. Estimates of patients with MS who experience walking impairment as the disease progresses range from 60% to more than 90%. The cause of walking impairment is multifactorial, with contributions from lower-limb weakness and incoordination, spasticity, sensory loss, imbalance, and fatigue. Walking impairment can have a negative effect on employment status, health care burden, the ability to perform activities of daily living, and health-related quality of life (HRQOL). More-tus, healthcare burden, the ability to perform activities of daily living impairment can have a negative effect on employment status. Maintenance of walking ability has been reported by patients with MS as the most highly valued bodily function.

The Timed 25-Foot Walk (T25-FW) is a short-format walking test commonly used in clinical practice and is one of the components of the Multiple Sclerosis Functional Composite (MSFC), an outcome measure frequently used in clinical trials to assess disability. The T25-FW is easy to administer, is useful for a range of walking disabilities, and correlates well with other measures of walking ability. Evaluation of changes in walking ability is important in clinical trials and clinical practice to assess disability progression. The importance of understanding the clinical meaning of change in the T25-FW and other components of the MSFC was emphasized by an expert panel convened by the National Multiple Sclerosis Society in May 2011. That panel recommended analysis of existing data to determine the feasibility of using the MSFC approach as a primary outcome measure for clinical trials in MS. The expert panel supported the use of the MSFC as a clinically meaningful outcome measure for MS clinical trials but recommended focusing on the component measures because the meaning of changes in composite z scores is not obvious, depends on the reference population, and is not comparable across studies. To this end, the task force recommended validating changes in the MSFC components in relation to known or interpretable changes in other assessments, particularly patient-reported outcome measures.

A clinically meaningful change is generally considered to be a change of sufficient magnitude that it is perceived by patients as being clinically important. One way to establish whether a change in a clinician-rated outcome is clinically meaningful is to determine the relationship between patient-reported outcomes and change in the clinician-rated outcome. Several previous studies assessed the clinical importance in T25-FW walking time using distribution or anchor-based approaches comparing the T25-FW with patient- or clinician-observed measures. Together, the findings suggest that a change of 20% or more in T25-FW walking time may be clinically meaningful. However, 1 study found no relationship between a worsening of 20% or more in T25-FW walking time and worsening on the Physical Impact subscale score of the patient-reported Multiple Sclerosis Impact Scale. Walking speed is more normally distributed than walking time, and the results of 2 studies that evaluated change in T25-FW walking speed suggest that improvements of 15% to 20% may be clinically meaningful. A better understanding of what defines a clinically meaningful change in T25-FW walking speed deserves further consideration.

The Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) and Safety and Efficacy of Natalizumab in Combination With Interferon Beta-1a in Patients With Relapsing-Remitting Multiple Sclerosis (SENTINEL) clinical trials in relapsing-remitting MS (RRMS) and the International MS Secondary Progressive Avonex Controlled Trial (IMPACT) study included the T25-FW and the patient-reported 36-Item Short Form Health Survey (SF-36) as a general health status measure of HRQOL. The objective of the present analysis was to evaluate the relationship between T25-FW walking speed and the Physical Component Summary (PCS) score of the SF-36 at baseline and changes in these measures over time to better understand the meaning of walking speed measured by the T25-FW.

### Methods

#### Clinical Trials

Descriptions of the patients and methods for the IMPACT, AFFIRM, and SENTINEL trials have been published. Briefly, the IMPACT trial (N = 436) was a 2-year, multicenter, randomized, double-blind trial of intramuscular (IM) interferon beta-1a, 60 μg administered weekly (n = 217), vs placebo (n = 219) in patients with SPMS. Enrolled patients ranged from 18 to 60 years of age, had clinically definite SPMS, and had an Expanded Disability Status Scale (EDSS) score of 3.5 to 6.5. The AFFIRM trial (N = 942) was a multicenter, randomized, double-blind, 30-month trial of natalizumab, 300 mg every 4 weeks (n = 627), vs placebo (n = 315). Enrolled patients ranged from 18 to 50 years of age and had a diagnosis of RRMS, an EDSS score of 0 to 5.0, and at least 1 documented relapse in the 12 months before trial entry. The SENTINEL trial (N = 1171) was a multicenter, randomized, double-blind, placebo-controlled, 30-month trial of natalizumab, 300 mg every 4 weeks, plus IM interferon beta-1a, 30 μg once weekly (n = 589), vs placebo every 4 weeks plus IM interferon beta-1a, 30 μg once weekly (n = 582). Enrolled patients ranged from 18 to 55 years of age and had a diagnosis of RRMS, an EDSS score of 0 to 5.0, at least 1 documented relapse, and had received treatment with IM interferon beta-1a once weekly for at least 12 months before randomization.

#### Assessments

The T25-FW, as part of the MSFC, was assessed at baseline and every 3 months in the IMPACT, AFFIRM, and SENTINEL trials. The SF-36, as part of the Multiple Sclerosis Quality of Life Inventory, was assessed at baseline and weeks 52 and 104 in the IMPACT trial and at baseline and weeks 24, 52, and 104 in the AFFIRM and SENTINEL trials.

For the T25-FW, patients were instructed to walk as fast as they could in a safe manner along a marked 25-foot course. The use of a walking aid was allowed. The time in seconds to complete each test was recorded, and the test was immediately repeated. The mean T25-FW walking time from the 2 as-
Walking Speed and HRQOL at Baseline

A total of 2549 patients constituted the combined patient population from the treatment groups of the IMPACT, AFFIRM, and SENTINEL trials. Baseline MS clinical characteristics differed among the pooled treatment groups, reflecting the different eligibility criteria among the trials (eTable in the Supplement). Most notably, the mean and median EDSS scores were higher and the proportion of patients with relapses in the year before trial entry was lower in the pooled treatment groups that included patients from the IMPACT trial vs those that included patients from the AFFIRM and SENTINEL trials. The mean baseline walking speeds by treatment group are shown in Table 1. The median walking speed in patients with MS (4.85 [range, 0.18-11.63] ft/s) was slower and the range broader than has been observed in healthy volunteers (6.76 [range, 4.81-8.93] ft/s) (to convert feet to meters, multiply by 0.3). The mean (SD) SF-36 PCS score was 41.6 (10.5) among all patients baseline to 2 years in T25-FW walking speed in the pooled placebo group was summarized in patients with and without a 5-point worsening in PCS score. In addition, the change in PCS score from baseline to 2 years was summarized for patients with the following percentage of changes in T25-FW walking speed: improvement of more than 20% and declines of at least 0%, 5%, 10%, 15%, 20%, 25%, and 30%.

Results

### Walking Speed and HRQOL at Baseline

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### Results

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and was lowest (31.7 [8.0]) in the treatment group that included only patients from the IMPACT trial, likely reflecting the effect of more severe disability on HRQOL (Table 1). Across the treatment groups, baseline SF-36 PCS scores were less than the reference score of 50.0 for the US general population.26

Among all patients in the 3 trials, a significant positive correlation ($r = 0.48; P < .001$) was observed between baseline walking speed and baseline SF-36 PCS scores (Figure 1 and Table 2). Among the SF-36 subscales, the strongest correlation was between the SF-36 Physical Functioning score and walking speed (Table 2). Significant correlations also were observed between baseline walking speed and SF-36 PCS and Physical Functioning scores in patients with less disability (EDSS score, <4) and more severe disability (EDSS score, ≥4) (Table 2).

**Change in Walking Speed and HRQOL From Baseline to 2 Years**

In the pooled placebo groups of the IMPACT and AFFIRM trials, the mean (SD) walking speed was 4.20 (1.87) ft/s at baseline and declined by 0.44 (0.91) ft/s at year 2. The mean (SD) SF-36 PCS score was 29.9 (10.8) at baseline and worsened by 1.0 (8.4) points at year 2 (Table 3). A significant correlation was observed between the change in SF-36 PCS score and the percentage of change in walking speed from baseline to 2 years in patients in the pooled placebo group ($r = 0.35; P < .001$). Significant correlations between the change in SF-36 PCS score to 2 years and percentage of change in walking speed also were observed in each active treatment group ($r = 0.13-0.28; P ≤ .005$).

Placebo-treated patients who experienced a clinically meaningful worsening (≥5-point decrease24 [27.5%]) in SF-36 PCS score from baseline to 2 years exhibited a mean decline of 21.8% in walking speed vs a mean decline of 5.4% in those without clinically meaningful worsening in SF-36 PCS score (Figure 2). When patients were grouped by incremental changes of 5% in walking speed, SF-36 PCS score declined in patients whose walking speed worsened and improved in patients who walked more than 20% faster (Figure 2). A decline in walking speed of 20% to 25% or more was associated with a mean decline in SF-36 PCS score of 5 points or more (Figure 3).

**Discussion**

In this post hoc analysis of data from 2 clinical trials of patients with RRMS and 1 trial of patients with SPMS, a significant correlation was observed between walking speed and SF-36 PCS score at baseline in patients with mild and more severe disability. In placebo-treated patients, a significant cor-

### Table 2. Correlation Between T25-FW Walking Speed and SF-36 Scores at Baseline

<table>
<thead>
<tr>
<th>SF-36 Scale Score</th>
<th>All</th>
<th>Patients With EDSS Score &lt;4</th>
<th>Patients With EDSS Score ≥4</th>
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<tr>
<td></td>
<td>No. of Patients</td>
<td>Correlation Coefficient*</td>
<td>P Value</td>
</tr>
<tr>
<td>PCS</td>
<td>2333</td>
<td>$r = 0.48$</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td>2333</td>
<td>$r &lt; 0.01$</td>
<td>.85</td>
</tr>
<tr>
<td>Subscales</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical Functioning</td>
<td>2383</td>
<td>$r = 0.60$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>2379</td>
<td>$r = 0.31$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>2373</td>
<td>$r = 0.22$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>General Health</td>
<td>2382</td>
<td>$r = 0.15$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vitality</td>
<td>2369</td>
<td>$r = 0.23$</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Social Functioning</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Mental Health</td>
<td>2364</td>
<td>$r &lt; 0.16$</td>
<td>&lt;.001</td>
</tr>
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</table>

Abbreviations: EDSS, Expanded Disability Status Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, 36-Item Short Form Health Survey; T25-FW, Timed 25-Foot Walk.

*Calculated as Pearson product moment correlation ($r$) or Spearman rank correlation ($ρ$). The Spearman correlation coefficient was used for the SF-36 subscales because the data were not normally distributed.
Table 3. Change From Baseline to 2 Years in T25-FW Walking Speed and SF-36 Scores

<table>
<thead>
<tr>
<th>Measure</th>
<th>Study Treatment</th>
<th>Placebo</th>
<th>IM Interferon Beta-1a</th>
<th>Natalizumab</th>
<th>Placebo + IM Interferon Beta-1a</th>
<th>Natalizumab + IM Interferon Beta-1a</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Patients</td>
<td>Mean (SD)</td>
<td>No. of Patients</td>
<td>Mean (SD)</td>
<td>No. of Patients</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>T25-FW speed, ft/s</td>
<td></td>
<td>458</td>
<td>-0.44 (0.91)</td>
<td>177</td>
<td>-0.48 (0.81)</td>
<td>562</td>
<td>-0.09 (0.91)</td>
</tr>
<tr>
<td>SF-36 PCS score</td>
<td></td>
<td>390</td>
<td>-1.0 (6.4)</td>
<td>126</td>
<td>0.1 (0.0)</td>
<td>518</td>
<td>1.1 (8.4)</td>
</tr>
<tr>
<td>SF-36 MCS score</td>
<td></td>
<td>390</td>
<td>-0.3 (11.2)</td>
<td>126</td>
<td>0.3 (9.2)</td>
<td>518</td>
<td>1.6 (10.9)</td>
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</table>

SF-36 Subscale scores

<table>
<thead>
<tr>
<th>SF-36 Subscale</th>
<th>Placebo</th>
<th>IM Interferon Beta-1a</th>
<th>Natalizumab</th>
<th>Placebo + IM Interferon Beta-1a</th>
<th>Natalizumab + IM Interferon Beta-1a</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>406</td>
<td>-5.0 (18.5)</td>
<td>131</td>
<td>-1.5 (18.3)</td>
<td>548</td>
<td>2.9 (18.3)</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>405</td>
<td>-0.9 (42.4)</td>
<td>131</td>
<td>3.2 (39.5)</td>
<td>543</td>
<td>7.1 (41.0)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>406</td>
<td>-2.3 (23.6)</td>
<td>129</td>
<td>-2.6 (22.9)</td>
<td>545</td>
<td>0.4 (23.6)</td>
</tr>
<tr>
<td>General Health</td>
<td>407</td>
<td>-0.1 (18.4)</td>
<td>131</td>
<td>2.2 (18.5)</td>
<td>549</td>
<td>3.2 (18.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>404</td>
<td>0.06 (20.5)</td>
<td>129</td>
<td>3.1 (18.7)</td>
<td>539</td>
<td>3.7 (20.6)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>405</td>
<td>-3.6 (24.6)</td>
<td>130</td>
<td>-1.6 (22.9)</td>
<td>547</td>
<td>4.1 (24.3)</td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>402</td>
<td>-2.8 (46.7)</td>
<td>130</td>
<td>0.9 (42.7)</td>
<td>535</td>
<td>4.7 (43.4)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>403</td>
<td>-1.0 (18.2)</td>
<td>129</td>
<td>-1.9 (15.7)</td>
<td>536</td>
<td>2.3 (17.4)</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscular; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, 36-Item Short Form Health Survey; T25-FW, Timed 25-Foot Walk.

Metric conversion factor: To convert feet to meters, multiply by 0.3.

Figure 2. Change in Walking Speed on the Timed 25-Foot Walk (T25-FW) in Placebo-Treated Patients With or Without Clinically Meaningful Worsening in 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS) Scores

Change in T25-FW walking speed was assessed from baseline to 2 years in patients in the pooled placebo group. Error bars represent SEM. Clinically meaningful worsening was defined as a decrease of 5 points or more in SF-36 PCS score from baseline to 2 years. Patients who experienced a clinically meaningful worsening in SF-36 PCS score from baseline to 2 years (n = 103) exhibited a mean decline of 21.8% in walking speed vs 5.4% in those without clinically meaningful worsening in SF-36 PCS score (n = 272).

Relation was observed between the change from baseline in SF-36 PCS score and the percentage of change in walking speed at 2 years. In placebo-treated patients, a decline in walking speed of 20% to 25% was associated with clinically meaningful worsening in SF-36 PCS scores during the 2-year period. Thus, the results from the present anchor-based analysis demonstrate that a decline in walking speed of 20% to 25% can be considered a clinically meaningful change.

Previous work suggested a relationship between gait impairment and declines in HRQOL in patients with MS. Increased severity of patient-reported walking and mobility problems was associated with worsening health status assessed using the EuroQol 5-Dimension Index and the Hamburg Quality of Life Questionnaire in multiple sclerosis. An indirect analysis using EDSS scores as a bridge showed that slower walking speed was associated with lower health utility scores in patients with MS. In addition, patient-perceived reductions in walking speed, assessed using responses to item 10 on the Multiple Sclerosis Impact Scale, were associated with reduced HRQOL as assessed using the EuroQol 5-Dimension Index and the 12-Item Short Form Health Survey. To our knowledge, the present report is the first direct analysis of the relationship between objectively measured walking speed on the T25-FW and HRQOL in patients with MS.

Results to date suggest that a deterioration of 20% or more in walking time on the T25-FW is clinically meaningful. Distribution-based approaches showed that the variability of repeated testing of the T25-FW walking time was generally less than 20%. In anchor-based studies, a 20% or greater increase in T25-FW walking time was associated with patient-reported walking difficulty, and changes (worsening or improvement) of 20% or more in T25-FW walking time were...
Walking speed in patients with multiple sclerosis

The present analysis demonstrated significant correlations between T25-FW walking speed and SF-36 PCS score at baseline and between declines in these measures over time. Furthermore, results using SF-36 PCS score as the anchor demonstrated that deterioration by 20% or more in T25-FW walking speed was associated with clinically meaningful worsening in patient-reported physical health status. Correlations between longitudinal changes in T25-FW walking speed and SF-36 PCS scores were weaker, but directionally the same, in the IM interferon beta-1a or natalizumab treatment groups vs the pooled placebo group. This finding might reflect in part the slower decline with treatment, which in turn would decrease the signal-to-noise ratio and thereby reduce the strength of the correlation. However, substantial worsening on the T25-FW in patients treated with IM interferon beta-1a remained, and therefore other items in the SF-36 PCS may be affected differen-

Figure 3. Change From Baseline in 36-Item Short Form Health Survey Physical Component Summary (SF-36 PCS) Scores by 2-Year Decline From Baseline in Walking Speed on the Timed 25-Foot Walk (T25-FW)

Placebo-treated patients were grouped by incremental 5% changes in T25-FW walking speed from baseline to 2 years. Error bars represent SEM. Dotted line represents the threshold for clinically meaningful change (≥5-point decrease) in SF-36 PCS score. The SF-36 PCS score declined in patients whose walking speed worsened and improved in patients who walked more than 20% faster. A decline in walking speed of 20% to 25% or more was associated with a clinically meaningful decline in SF-36 PCS score.

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tially by treatment with this agent. The reason for the differences in the magnitude of the correlations among the treatment groups deserves further exploration.

The more normal distribution of walking speed compared with walking time raises the question of whether T25-FW walking time in the MSFC should be transformed into walking speed before calculating z scores. The advisability of this approach deserves further consideration. Additional studies are needed to confirm the thresholds for clinically meaningful improvement and worsening in T25-FW walking speed in patients with RRMS and SPMS and to evaluate the effects of treatment and MS disease variables (eg, EDSS progression, relapse status) on the relationship between walking speed and HRQOL. In addition, a natural extension of this study would be to evaluate the relationship between SF-36 PCS score and the 9-hole peg test,32 a component of the MSFC that assesses upper limb function.

Conclusions

In patients with MS, walking speed measured using the T25-FW correlated with the SF-36 PCS scores such that a decline in walking speed of 20% to 25% corresponded to a clinically meaningful worsening of SF-36 PCS scores. A 20% to 25% decline in walking speed may be a clinically meaningful threshold for defining worsening using the T25-FW in MS clinical trials and for monitoring patients in clinical settings.

REFERENCES