The Unseen Progress: How PROs May Overlook the Value of Slowing Degenerative Decline

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BACKGROUND

Disease trajectories and treatment expectations vary: Some conditions focus on improving symptoms or curing the disease, while others aim to prevent worsening or manage symptoms, influencing patient expectations (Figure 1)

In diseases targeting improvement, patient-reported outcomes (PROs) capture treatment impact as patients can reflect on symptom relief or enhanced quality of life

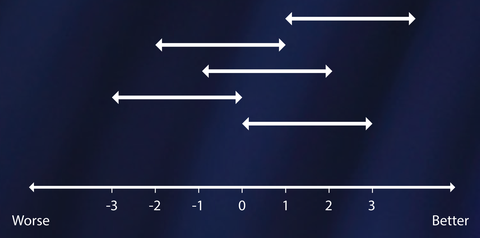
In progressive neurodegenerative diseases (eg, Alzheimer's disease [AD], amyotrophic lateral sclerosis [ALS], and multiple sclerosis [MS]), where decline is gradual and irreversible, patients often start with minimal impairment[1]

Treatment goals in progressive diseases focus on preserving function and slowing irreversible decline, rather than improvement[1]

Patients may not yet perceive impairment or meaningful change, making it challenging to recognize or report benefit from slowed disease progression[1]

PRO instruments may not fully capture benefits in progressive conditions, as they are often designed to detect improvement, limiting sensitivity to stability or delayed decline

Figure 1: Patient-Relevant Meaning of Uniform 3-Point Differences



OBJECTIVE

To examine the relationship between clinical outcomes and PROs in degenerative diseases, focusing on patient perceptions of treatments that slow progression

METHODS

The pivotal trials of the most recent Food and Drug Administration (FDA)-approved treatments for 4 pre-selected degenerative diseases were analyzed[2-9] (Table 1)

For each condition, we evaluated the reported clinical outcomes and corresponding PROs, with a focus on whether PROs aligned with the observed clinical benefits in slowing disease progression

Table 1: Overview of Most Recent FDA-Approved Treatments and Pivotal Trials for Four Degenerative Diseases

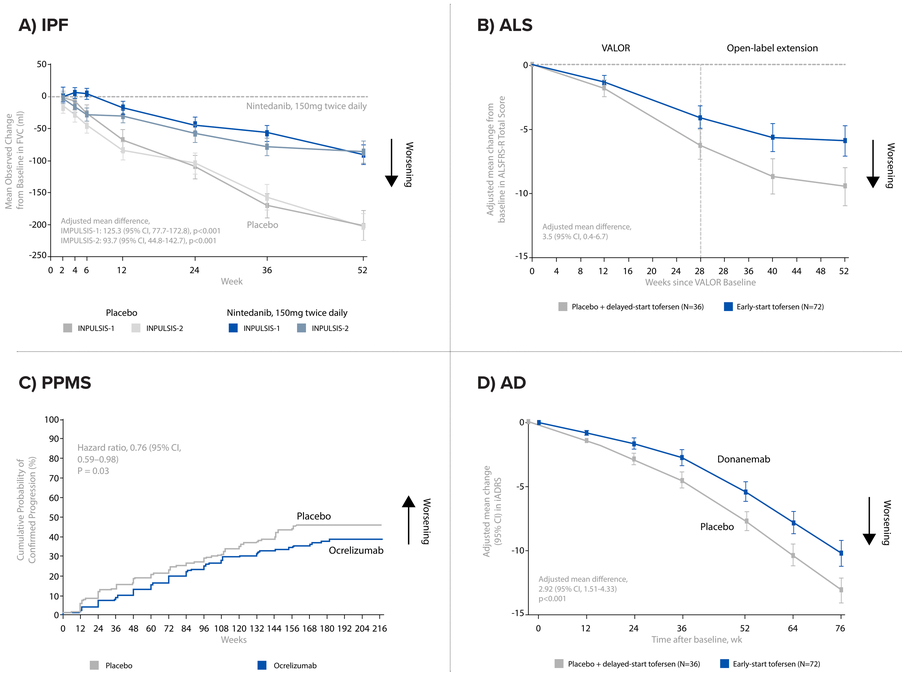
Disease	Drug	FDA-approval	Trial
Idiopathic Pulmonary Fibrosis (IPF)	Nintebanib	2014[2]	INPULSIS-1 & -2 Phase 3[3]
Amyotrophic Lateral Sclerosis (ALS)	Tofersen	2023[4]	VALOR Phase 3[5]
Primary Progressive Multiple Sclerosis (PPMS)	Ocrelizumab	2017[6]	ORATORIO Phase 3[7]
Alzheimer's Disease (AD)	Donanemab-azbt	2024[8]	TRAILBLAZER ALZ 2 Phase 3[9]

RESULTS

All 4 drugs were approved based on statistically significant differences vs controls in primary clinical endpoints of disease progression in pivotal trials[3,5,7,9] (Figure 2)

- The primary clinical outcome was either clinician-reported outcomes (75%) or surrogate biomarkers (25%)
- Despite statistically significant differences between the treatment and control groups, both groups showed a decline in disease progression from baseline for all 4 drugs

Figure 2: Primary Endpoints from Pivotal Trials of Four FDA-Approved Treatments



Among the 4 pivotal trials, treatment benefit in PROs was observed only with tofersen for ALS using the EuroQol-5 Dimension (EQ-5D) scale. However, both treatment and control groups showed a decline in EQ-5D score from baseline[3,5,7,9] (Table 2)

- A total of 3 generic PROs and 2 disease-specific PROs were assessed across the 4 trials
- No other statistically significant differences were observed for either generic or disease-specific PROs across the trials
- However, in AD, a treatment benefit was seen with donanemab-azbt using the observer-reported outcome, Alzheimer's Disease Cooperative Study - instrumental activities of daily living (ADCS-iADL) measure

Table 2: Comparison of Statistical Differences Between Clinical Endpoints and PROs Across Four Degenerative Diseases

Disease: Drug	Endpoint Type	Endpoint	Between Group Difference	Change from Baseline (Drug)	Change from Baseline (Control)	Change from baseline > MCID
IPF: Nintedanib[3]	Surrogate (primary)	FVC	INPULSIS-1: Yes; **125.3 (77.7 to 172.8)**	INPULSIS-1: -114.7	INPULSIS-1: -239.9	NR
			INPULSIS-2: **Yes; 93.7 (44.8 to 142.7)**	INPULSIS-2: -113.6	INPULSIS-2: -207.3	
	Disease specific PRO	SGRQ	Symptoms domain: No; -1.85 (-4.22 to 0.51)	1.82	3.67	No
			Activity domain: **Yes; -2.30 (-4.23 to -0.37)**	4.24	6.54	Yes
			Impact domain: No; -1.15 (-3.08 to 0.78)	3.83	4.98	Yes for control group
ALS: Tofersen[5]	ClinRO (primary)	ALSFRS-R	**Yes; 3.5 (0.4 to 6.7)**	-6.0	-9.5	NR
	Generic PRO	EQ-5D-5L Utility	**Yes; 0.2 (0.13 to 0.21)**	-0.1	-0.3	NR
	Generic PRO	FSS	No; -3.8 (-9.03 to 1.38)	1.3	5.1	NR
PPMS: Ocrelizumab[7]	ClinRO (primary)	12-week confirmed disability progression	**Yes; 0.76 (0.59 to 0.98)**	32.9%	39.3%	NR
	Generic PRO	SF-36 physical component	No; 0.38 (-1.05 to 1.80)	-0.73 (-1.66 to 0.19)	-1.11 (-2.39 to 0.18)	NR
AD: Donanemab-azbt[9]	ClinRO (primary)	iADRS score	**Yes; 2.92 (1.51 to 4.33)**	**-10.19 (-11.22 to -9.16)**	**-13.11 (-14.10 to -12.13)**	Yes
	Disease-specific ObsRO	ADCS-iADL (caregiver)	**Yes; 1.80 (0.84 to 2.57)**	**-4.42 (-5.05 to -3.80)**	**-6.13 (-6.72 to -5.53)**	NR

CONCLUSION & NEXT STEPS

PRO measures may not fully reflect treatment benefits in degenerative diseases. Future research should explore how patient experience data can better reflect these benefits. It is important to consider whether a fixed minimal clinically important difference (MCID) score is appropriate for both improvement and worsening. Personalized endpoints, such as goal attainment scaling, can help manage expectations and highlight outcomes that matter most to patients.

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ABBREVIATIONS IN TABLES AND FIGURES

AD: Alzheimer's Disease; ADCS-iADL: Alzheimer's Disease Cooperative Study - instrumental activities of daily living; ALS: Amyotrophic Lateral Sclerosis; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ClinRO: Clinician reported outcome; EQ-5D: EuroQol-5 Dimension; FDA: Food and Drug Administration; FSS: Fatigue Severity Scale; FVC: Forced vital capacity; iADRS: Alzheimer's Disease Rating Scale; IPF: Idiopathic Pulmonary Fibrosis; SGRQ: St. George's Respiratory Questionnaire; MCID: Minimal clinically important difference; MS: Multiple Sclerosis; PGI-C: Patient Global Impression of Change; PPMS: Primary Progressive Multiple Sclerosis; PRO: Patient reported outcome; SF-36: Short Form (36) Health Survey

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