**Background:** In the AFFIRM trial, natalizumab reduced sustained visual loss as measured by low-contrast letter acuity (LCA), but not high-contrast visual acuity (HCA). Natalizumab was associated with improvements in disability and quality of life. We sought to determine whether visual function improvement could also be demonstrated. **Objectives:** To analyze the probability of visual improvement and its association with treatment status in the pivotal, phase 3 trial of natalizumab. **Methods:** Binocular vision testing was performed for HCA and LCA. Cumulative probabilities of visual improvement, sustained over 12 weeks, were determined for increases in score by 1 line (5 letters) and 2 lines (10 letters). Improvement by 7 letters was also examined as a threshold, since this represents the upper limit of test-retest variability based on reliability studies of LCA. **Results:** The probability of visual improvement, defined as ≥7-letter score increase from baseline, sustained for 12 weeks, was greater for natalizumab (n = 627) than for placebo (n = 314). This was observed for LCA at 2.5% contrast (21% vs. 13% with improvement, hazard ratio = 1.57, P = .012) and 1.25% contrast (32% vs. 24%, hazard ratio = 1.39, P = .014, Cox proportional hazards models). A much lower probability of improvement (≈6%) in HCA was demonstrated, with no differences between treatment groups. Natalizumab treatment was associated with greater proportions of patients showing improvement from baseline for at least 8 of 10 study visits by LCA (2.5%: 23% vs. 15% for placebo, P = .013; 1.25%: 28% vs. 23% for placebo, P = .043). There was a greater degree of improvement across all visits for natalizumab than for placebo by using 2.5% contrast (P = .003), with a trend for 1.25% (P = .055). Probabilities of improvement at threshold levels below (5 letters) and above (10 letters) test-retest variability did not show treatment differences. **Conclusions:** Natalizumab treatment is associated with sustained visual improvement by some measures of visual function; this improvement is particularly well captured by the 2.5% contrast chart. HCA was less sensitive and failed to capture treatment effects on improvements in visual function.

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