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Long-term treatment effects of inotersen on health-related quality of life in patients with hATTR amyloidosis with polyneuropathy: Analysis of the open-label extension of the NEURO-TTR trial

Chafic Karam[1], Duncan Brown[2], Min Yang[3], Nicolae Done[3], Jing Jing Zhu[3], Alexandra Greatsinger[3], Ana Bozas[2], Montserrat Vera-Llonch[2], James Signorovitch[3]
Affiliations expand

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Abstract

Introduction/aims: Hereditary transthyretin-mediated amyloidosis with polyneuropathy (hATTR-PN) progressively affects patients' functionality and compromises health-related quality of life (HRQL). The aim of this study was to quantify the projected long-term treatment effects of inotersen vs placebo on HRQL measures.

Methods: The inotersen phase 2/3 randomized, double-blind, placebo-controlled trial NEURO-TTR (NCT01737398, 65 weeks) and its subsequent open-label extension (OLE; NCT02175004, 104 weeks) included 172 (112 inotersen and 60 placebo) patients. Placebo double-blind period and overall inotersen-inotersen (double-blind/OLE) treatment period (170 weeks) data were used to extrapolate the long-term placebo-placebo effect using mixed-effects models with repeated measures. Changes from baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) and 36-Item Short Form Health Survey version 2 (SF-36v2) in hATTR-PN were estimated. Differences in

changes were compared between the inotersen-inotersen and extrapolated placebo-placebo arms.

Results: Inotersen-inotersen patients maintained their HRQL with an observed change ranging from 10.3% improvement (Norfolk QoL-DN item "Pain kept you awake at night") to 11.6% deterioration (SF-36v2 Activities of Daily Living subdomain). The extrapolated placebo-placebo results suggest greater deterioration over time compared with inotersen-inotersen treatment on Norfolk QoL-DN total score (23.6; 95% confidence interval [CI], 8.9-38.3; P < .01), Activities of Daily Living (4.6; 95% CI, 2.0-7.3; P < .001), and "Pain kept you awake at night" (1.2; 95% CI, 0.4-1.9; P < .01). Similarly, greater deterioration was expected for the SF-36v2 Physical Component Summary (8.0; 95% CI, 3.2-12.8, P < .01), Bodily Pain (7.8; 95% CI, 2.0-13.5; P < .01), and Physical Functioning (10.6; 95% CI, 5.5-15.6; P < .0001).

Discussion: Long-term (>3 years) inotersen treatment was associated with slowing and, in some domains, halting of deterioration in key HRQL outcome measures, particularly physical functioning and pain.

Keywords: 36-item Short-Form Health Survey; Norfolk Quality of Life---Diabetic Neuropathy; amyloidosis; inotersen; neuropathic pain; physical functioning; quality of life; transthyretin.

Practice Guideline

Medicina (B Aires)

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[Practice guideline for the treatment of familial amyloid polyneuropathy]

[Article in Spanish]

Marcelina Carretero[1], María S Sáez[2], María L Posadas-Martínez[3], María A Aguirre[4], Patricia Sorroche[2], Agustina Negro[5], Cristian R Calandra[6], Valeria Salutto[7], Andrea Lautre[8], Eugenia Conti[9], Luciana León-Cejas[9], Ricardo Reisin[9], Elsa M Nucifora[10], Marcelo Rugiero[11]
Affiliations expand

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Free article

Abstract

in English, Spanish

This clinical practice guideline for the treatment of familial amyloid polyneuropathy is based on the best available evidence of clinical effectiveness. A list of questions was generated with a PICO format focused on the effectiveness and safety of the treatment of familial amyloid polyneuropathy. The search was carried out in PubMed, Cochrane and Epistemonikos. The levels of evidence and grades of recommendation were based on the GRADE system. Recommendations were graded according to their direction and their strength and were evaluated with the GLIA tool for their implementation. In patients with familial amyloid polyneuropathy and stage I and II neuropathy, it is suggested: inotersen 300 mg subcutaneous weekly or patisirán 0.3 mg/kg intravenously once every 3 weeks, since they probably stabilize or slow the progression of neuropathy and worsening quality of life (moderate quality of evidence; strength of recommendation weak). In patients with familial amyloid polyneuropathy and stage I neuropathy, treatment with tafamidis 20 mg orally, once a day, is suggested, as it could slow the progression of neuropathy and worsen quality of life (low quality of evidence; strength of recommendation weak). In patients with familial amyloid polyneuropathy and symptomatic neuropathy and in the absence of other treatments with approved efficacy, treatment with oral diflunisal 250 mg twice daily is suggested, as it could prevent the progression of neuropathy (quality evidence low; strength of recommendation weak).

Keywords: GRADE approach; amyloidosis; health planning guideline; recommendations; treatment outcome.

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Factors associated with increased health-related quality-of-life benefits in hereditary transthyretin amyloidosis polyneuropathy patients treated with inotersen

Chafic Karam[1], Duncan Brown[2], Min Yang[3], Nicolae Done[3], Ibou Dieye[3], Ana Bozas[2], Montserrat Vera Llonch[2], James Signorovitch[3]
Affiliations expand

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Abstract

Introduction/aims: Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a genetic condition associated with significant morbidity and mortality. In this study we aimed to identify patient subgroups exhibiting the greatest health-related quality of life (HRQL) benefit from inotersen treatment.

Methods: We examined data from the inotersen phase 2/3 randomized, controlled trial for ATTRv-PN, NEURO-TTR (NCT01737398, 66 weeks). LASSO regression models predicted changes in Norfolk QoL-DN total score (TQoL, range -4 to 136; higher scores indicate poorer HRQL) from baseline in the inotersen and placebo arm, respectively. Individualized efficacy scores (ES) were calculated as differences between predicted change scores had patients received inotersen vs placebo. Patients were ranked by ES to define the greatest-benefit subpopulation (top 50%). Characteristics of the top 50% and bottom 50% of patients were compared.

Results: The overall mean ± standard deviation TQoL change was -0.20 ± 19.13 for inotersen (indicating no change) and 10.77 ± 21.13 for placebo (indicating deterioration). Within the highest-benefit patients, mean TQoL change was -11.03 ± 17.06 (improvement) for inotersen and 11.24 ± 22.97 (deterioration) for placebo (P < .001). Compared with the overall population, patients in the greatest-benefit subpopulation were younger, more likely to have polyneuropathy disability (PND) scores 1 or 2, less likely to have received prior tafamidis or diflunisal treatment, and more likely to have Val30Met mutations and higher (worse) baseline TQoL.

Conclusions: Patients who were younger and/or at earlier polyneuropathy stages experienced greater HRQL benefits from inotersen over 66 weeks. These findings underscore the need for early diagnosis and treatment initiation, especially among more severely affected patients in early stages of ATTRv-PN.

Keywords: health-related quality of life; hereditary transthyretin amyloidosis; individualized medicine; inotersen; polyneuropathy.

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Long-term efficacy and safety of inotersen for hereditary transthyretin amyloidosis: NEURO-TTR open-label extension 3-year update

Thomas H Brannagan[1], Teresa Coelho[2], Annabel K Wang[3], Michael J Polydefkis[4], Peter J Dyck[5], John L Berk[6], Brian Drachman[7], Peter Gorevic[8], Carol Whelan[9], Isabel Conceição[10], Violaine Plante-Bordeneuve[11], Giampaolo Merlini[12], Laura Obici[12], Josep Maria Campistol Plana[13], Josep Gamez[14], Arnt V Kristen[15], Anna Mazzeo[16], Luca Gentile[16], Arvind

Narayana[#17], Kemi Olugemo[#17], Peter Aquino[#17], Merrill D Benson[18], Morie Gertz[5], NEURO-T. T. R. Open-Label Extension Investigators
Affiliations expand

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Abstract

Background: Hereditary transthyretin amyloidosis (hATTR/ATTRv) results from the deposition of misfolded transthyretin (TTR) throughout the body, including peripheral nerves. Inotersen, an antisense oligonucleotide inhibitor of hepatic TTR production, demonstrated a favorable efficacy and safety profile in patients with the polyneuropathy associated with hATTR in the NEURO-TTR (NCT01737398) study. We report longer-term efficacy and safety data for inotersen, with a median treatment exposure of 3 years.

Methods: Patients who satisfactorily completed NEURO-TTR were enrolled in its open-label extension (OLE) study. Efficacy assessments included the modified Neuropathy Impairment Score + 7 (mNIS + 7), Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire total score, and the Short Form 36 (SF-36v2) Health Survey Physical Component Summary score. Safety and tolerability were also assessed. Efficacy is reported for patients living in Europe and North America (this cohort completed the study approximately 9 months before the remaining group of patients outside these regions); safety is reported for the full safety dataset, comprising patients living in Europe, North America, and Latin America/Australasia. This study is registered with ClinicalTrials.gov, identifier NCT02175004.

Results: In the Europe and North America cohort of the NEURO-TTR study, 113/141 patients (80.1%) completed the study, and 109 patients participated in the OLE study. A total of 70 patients continued to receive inotersen (inotersen-inotersen) and 39 switched from placebo to inotersen (placebo-inotersen). The placebo-inotersen group demonstrated sustained improvement in neurological disease progression as measured by mNIS + 7, compared with predicted worsening based on projection of the NEURO-TTR placebo data (estimated natural history). The inotersen-inotersen group demonstrated sustained benefit, as measured by mNIS + 7, Norfolk QoL-DN, and SF-36v2, compared with estimated natural history as well as compared with the placebo-inotersen group. With a maximum exposure of 6.2 years, inotersen was not associated with any additional

safety concerns or increased toxicity in the OLE study. Platelet and renal monitoring were effective in reducing the risk of severe adverse events in the OLE study.

Conclusion: Inotersen treatment for > 3 years slowed progression of the polyneuropathy associated with hATTR, and no new safety signals were observed.

Keywords: Clinical trial; Familial amyloid polyneuropathy; Hereditary transthyretin amyloidosis; Inotersen; Peripheral neuropathies; Polyneuropathy.