An 8-week, open-label, dose-finding study of nimodipine for the treatment of progranulin insufficiency from *GRN* gene mutations

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Abstract

**Introduction**: Frontotemporal lobar degeneration—causing mutations in the progranulin (*GRN*) gene reduce progranulin protein (PGRN) levels, suggesting that restoring PGRN in mutation carriers may be therapeutic. Nimodipine, a Food and Drug Administration–approved blood-brain barrier-penetrant calcium channel blocker, increased PGRN levels in PGRN-deficient murine models. We sought to assess safety and tolerability of oral nimodipine in human *GRN* mutation carriers.

**Methods**: We performed an open-label, 8-week, dose-finding, phase 1 clinical trial in eight *GRN* mutation carriers to assess the safety and tolerability of nimodipine and assayed fluid and radiologic markers to investigate therapeutic endpoints.

**Results**: There were no serious adverse events; however, PGRN concentrations (cerebrospinal fluid and plasma) did not change significantly following treatment (percent changes of \(-5.2 \pm 10.9\%\) in plasma and \(-10.2 \pm 7.8\%\) in cerebrospinal fluid). Measurable atrophy within the left middle frontal gyrus was observed over an 8-week period.

**Discussion**: While well tolerated, nimodipine treatment did not alter PGRN concentrations or secondary outcomes.

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1. Introduction

Mutations in the progranulin gene (GRN) are a common cause of inherited frontotemporal dementia (FTD). GRN mutations cause haploinsufficiency, with only one functional copy of the gene remaining. Progranulin protein (PGRN) levels are less than 50% from birth [1–3]. Thus, therapeutic approaches have focused on increasing PGRN levels, either by increasing transcription from the normal allele [4,5] or by modulating posttranslational mechanisms [6,7].

Promising preclinical data in heterozygous Grn mice suggested that nimodipine might restore PGRN levels in humans with GRN mutations. As PGRN levels are stable over both short and long periods (1 week to 2 years) in GRN mutation carriers [8] as well as various disease and control populations [9], PGRN levels alone are suitable endpoints for trials. We tested the effects of modulators of calcium homeostasis on PGRN levels in cultured cells and found that reducing intracellular calcium by blocking calcium channels increased PGRN secretion. We focused on nimodipine, a Food and Drug Administration–approved drug at a dose of 360 mg per day, we chose a titration to 360 mg or maximum tolerated dose. Nimodipine was titrated every week as follows: 30 mg orally TID, 60 mg TID, 90 mg TID, and 90 mg QID and maintained at this dose for 4 weeks. All subjects attempted to titrate to the full 360 mg per day dose (Supplementary Fig. 3).

2. Methods

2.1. Study oversight

This study was approved under local institutional review board’s supervision, registered at ClinicalTrials.gov (NCT01835665). Informed consent was obtained from patients and, when applicable, caregivers.

2.2. Study design and enrollment

The target enrollment was eight asymptomatic and/or symptomatic carriers of known FTD-causing GRN mutations (Supplementary Fig. 2). Participants were required to be aware of their mutation status before screening. Participants were enrolled from March 2013 until January 2015. Inclusion and exclusion criteria are listed in Supplementary Materials.

Because nimodipine is a Food and Drug Administration–approved drug at a dose of 360 mg per day, we chose a titration to 360 mg or maximum tolerated dose. Nimodipine was titrated every week as follows: 30 mg orally TID, 60 mg TID, 90 mg TID, and 90 mg QID and maintained at this dose for 4 weeks. All subjects attempted to titrate to the full 360 mg per day dose (Supplementary Fig. 3).

2.3. Outcomes

Primary outcomes were safety and tolerability of nimodipine and identification of the optimal nimodipine dose for long-term efficacy studies in GRN mutation carriers. Safety was measured by the number of treatment emergent adverse events (listed by detailed MedDRA term [www.meddra.org]), routine clinical, laboratory, and electrocardiogram assessments. Secondary outcomes were change from baseline concentration of plasma PGRN or CSF PGRN, plasma PGRN-related inflammatory markers (c-reactive protein [CRP], erythrocyte sedimentation rate [ESR]), CSF neurodegeneration proteins (neurofilament light chain [NfL], amyloid β 42 [Aβ42], tau), blood and CSF cytokines (interleukin-10 [IL-10], IL-2, IL-6, IL-8, and tumor necrosis factor α [TNFα]), and volumetric magnetic resonance imaging (MRI).

2.4. Plasma and CSF sampling and analysis

PGRN was measured by A&G Pharma (Columbia, MD) using a proprietary enzyme-linked immunosorbent assay that detects full-length PGRN. TNFα was measured by Quanterix (Lexington, MA). Tau, phospho-tau181, and Aβ42 levels were analyzed using the xMAP multiplex immunoassay/Luminex analyzer (INNO-BIA AlzBio3; Fujirebio). NfL levels were measured using the UmanDiagnostics kit (Umeå, Sweden). Proinflammatory cytokines were measured in plasma and CSF using a V-PLEX human proinflammatory 10-Plex kit from Meso Scale Discovery (Rockville, MD). Nonparametric measures (Mann-Whitney U) were used to compare mean baseline versus 8-week or early termination values of the secondary clinical and laboratory measures.

2.5. Brain imaging

MRI was performed at screening and completion of the study using a 3T Siemens scanner [11]. MP-RAGE scans for both time points for a given subject were registered to
Table 1  
Characteristics of study participants

| Clinical phenotype (clinicians’ impression) | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 | Subject 7 | Subject 8 | Mean |
|--------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|------|
| CDR-SB                                     | nfvPPA    | Asymptomatic | Asymptomatic | bvFTD   | bvFTD | Asymptomatic | bvFTD | Asymptomatic | -   |
| MMSE                                      | 0         | 0.5       | 0         | 12       | 4       | 0         | 2         | 0         | 2.3  |
| Completed 8 weeks?                         | Yes       | Yes       | Yes       | Yes      | Yes     | Yes       | Yes       | No        | -    |
| Max dose achieved (mg)                     | 360       | 360       | 360       | 180–270  | 360     | 360       | 360       | 180       | -    |
| Plasma GRN ng/mL, (% change)               | 1.1 (21)  | 1.4 (19)  | -12.6 (−53) | -0.2 (−2) | 4.9 (23) | -1.5 (−16) | -3.4 (−27) | -         | -1.47 ± 2.1 (−5.2 ± 10.9) |
| Plasma ESR mm/hour, (% change)             | 2 (40) nd | 0 (0)     | 19 (91)   | 24 (500) | 5 (−31)  | -          | -         | -         | -    |
| Plasma CRP mg/L, (% change)                | 0.4 (14)  | −0.1 (−1) | 1.2 (92)  | 1.7 (39) | 6.8 (145) | 5.9 (590) | 0.1 (6)   | -         | 1.8 ± 1.2 (115.4 ± 62.5) |
| CSF GRN ng/mL, (% change)                  | −0.07 (−13) | 0.06 (27) | −0.15 (−18) | −0.2 (−27) | −0.28 (−41) | 0.06 (15) | −0.05 (−12) | −0.08 (−17) | −0.09 ± 0.04 (−10.7 ± 7.8) |
| CSF NfL pg/mL, (% change)                  | 211.8 (5) | −39.5 (−12) | −7.4 (0)  | 750.6 (5) | −654.5 (−8) | 71.4 (9)  | −499.9 (−5) | −77.9 (−7) | −30.68 ± 151.8 (−1.4 ± 2.5) |
| CSF Aβ42 pg/mL, (% change)                 | −8.7 (−1) | −81.6 (−15) | 76.8 (11) | 19.7 (4)  | −46.3 (−14) | −35.4 (−6) | −58.3 (−12) | −103.9 (−19) | −29.70 ± 20.5 (−6.5 ± 3.6) |
| CSF Tau pg/mL, (% change)                  | 4.2 (7)   | −4.2 (−14) | −0.4 (−1) | 25.8 (25) | 10.0 (12) | −6.7 (−16) | 2.2 (−3)  | 2.0 (5)   | 3.59 ± 3.7 (1.9 ± 4.8) |
| CSF P-tau pg/mL, (% change)                | −1.7 (−7) | 5.8 (31)  | −0.8 (−3) | −3.0 (−13) | 2.0 (17)  | −8.0 (−34) | 7.8 (89)  | 1.6 (13)  | 0.48 ± 1.8 (11.6 ± 13.1) |
| CSF IL-10 pg/mL, (% change)                | 0.03 (6)  | 0.001 (−1) | 0.005 (−5) | 0.01 (11) | −0.01 (−15) | -          | 0.003 (4) | 0.04 (65) | 0.00 ± 0.1 (9.1 ± 9.8) |
| CSF IL-2 pg/mL, (% change)                 | 0.01 (10) | 0.01 (31)  | 0.03 (62) | −0.02 (−33) | 0 (9)    | -          | 0.03 (36) | 0.01 (14) | 0.01 ± 0.01 (18.5 ± 11.2) |
| CSF IL-6 pg/mL, (% change)                 | 0.11 (6)  | −0.15 (−11) | −0.04 (−3) | 0.07 (7)  | 0.14 (13) | -          | 0.11 (16) | 0.06 (8)  | 0.04 ± 0.04 (5.1 ± 3.5) |
| CSF IL-8 pg/mL, (% change)                 | 3.82 (5)  | 1.24 (4)  | −0.38 (−1) | 6.74 (9)  | 4.65 (11) | -          | −1.72 (−6) | −0.16 (0) | 2.0 ± 1.17 (3.1 ± 2.2) |
| CSF TNF pg/mL, (% change)                  | 0.00 (0)  | 0.00 (−38) | 0.02 (14)  | −0.07 (−16) | 0.04 (42) | -          | 0.00 (1)  | 0.01 (9)  | 0.01 ± 0.02 (1.4 ± 9.4) |

Abbreviations: Aβ42, amyloid β; CDR-SB, Clinical Dementia Rating—sum of boxes; CSF, cerebrospinal fluid; GRN, progranulin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MMSE, Mini-Mental State Examination; nd, not determined; NfL, neurofilament light chain; P-tau, phospho-tau; TNFα, tumor necrosis factor α.

NOTE: Age and gender were not shown to maintain participant confidentiality.
one another using the serial longitudinal anatomical MRI package in SPM12 [12], and the procedures outlined elsewhere [13].

3. Results

3.1. Preclinical studies

Cultured cellular models revealed that cytosolic calcium levels affected the secreted PGRN levels (Supplementary Fig. 1). Two-week treatment with nimodipine elevated hippocampal PGRN levels in both wild-type (P < .001) and Grn+/− mice (P < .05) compared to vehicle-treated mice (Supplementary Fig. 1).

3.2. Demographics

Eight GRN mutation carriers were enrolled in the trial (Table 1), with a median age of 57.3 years; 50% were male. They included three behavioral-variant FTD (bvFTD), one nonfluent-variant primary progressive aphasia (nvPPA), and four asymptomatic individuals. One self-reported asymptomatic participant had a 0.5 in judgment (nfvPPA), and four asymptomatic individuals. One nonfluent-variant primary progressive aphasia (bvFTD) participant discontinued treatment early at week 5 due to dizziness, palpitations, and malaise. Another discontinued due to edema. There were no serious adverse events. Forty-three adverse events were reported; the most common included edema (12 reports), headache (3), and dizziness (3). There were also two reports of arrhythmia and lassitude. There were single reports of upper respiratory infection, flu-like symptoms, syncope, redness on legs, depression, insomnia, worsening of asthma, and urinary tract infection.

3.3. Safety and tolerability

Two of the eight participants (25%) were unable to titrate to the maximum dose of 360 mg per day (Table 1). One participant discontinued treatment early at week 5 due to dizziness, palpitations, and malaise. Another discontinued due to edema. There were no serious adverse events. Forty-three adverse events were reported; the most common included edema (12 reports), headache (3), and dizziness (3). There were also two reports of arrhythmia and lassitude. There were single reports of upper respiratory infection, flu-like symptoms, syncope, redness on legs, depression, insomnia, worsening of asthma, and urinary tract infection.

3.4. Fluid biomarkers

PGRN concentrations, in plasma and CSF, did not change from baseline after nimodipine treatment (percent changes of −5.2 ± 10.9% [mean ± standard error mean] in plasma and −10.2 ± 7.8% in CSF) (Table 1 and Fig. 1A and 1B).

CSF levels of three neurodegenerative disease–associated proteins, NfL, Aβ42, and tau (both total tau and phospho-tau) did not change significantly after nimodipine treatment (Table 1). Levels of CSF NfL (P = .0002, Mann-Whitney U) and tau (P = .0002, Mann-Whitney U) at baseline correlated with disease severity as measured by CDR-SB, with the highest levels of NfL and tau observed in subjects with the highest CDR-SB score (Fig. 1C and 1D).

Of 10 cytokines measured in CSF, five were detectable (IL-10, IL-2, IL-6, IL-8, and TNFα), and none exhibited a significant change following nimodipine treatment (Table 1).

3.5. Volumetric MRI

Longitudinal structural MRI differences were determined by performing a one-sample t-test on the longitudinal Jacobian gray matter change maps. Six subjects were analyzed (mean age = 56.2 years, range 32.5–69.0; 4 females; mean interscan interval = 50.7 days, range 29–70). The resultant map was corrected with a joint height/extent threshold of P < .001 (no significant reductions were detected at a more stringent threshold of P < .05, family-wise error corrected). There was one significant cluster of gray matter loss in the left middle frontal gyrus. The rate of change in this cluster revealed that the effect was driven by four subjects with annualized rates of gray matter loss between 1% and 2% (Fig. 1).

4. Discussion

PGRN deficiency causes FTD; therefore, treatments that restore PGRN levels are of high therapeutic interest. We found that oral nimodipine increased mouse hippocampal PGRN concentrations but failed to increase human PGRN levels in plasma and CSF. In an 8-week, open-label trial, nimodipine was safe and well tolerated in GRN mutation carriers, but no effects of nimodipine were noted on secondary outcome measures, including concentrations of PGRN in blood and CSF, CSF NfL, CSF Aβ42, CSF total tau, CSF phospho-tau, plasma ESR, plasma CRP, or CSF cytokines (IL-10, IL-2, IL-6, IL-8, and TNFα). Although there were no clear effects on volumetric MRI measurements by nimodipine, there was volume loss noted in severely affected patients. Reasons for the discrepancy between rodents and humans are unknown and may be related to many factors, including exposure, dose, timing, and interspecies difference in responsiveness.

Of the six participants with MRIs conducted before and after treatment, three were asymptomatic and three were symptomatic. The most severely affected cases displayed the greatest decrease in volume over the trial period; a change that would extrapolate to a 1%–2% loss in the volume of the left frontal region annually, if constant. This rate is slightly less than reported for whole-brain atrophy in a comparably sized group of GRN mutation carriers assessed with MRI scans over 2 years [14]. Intermediate volume loss was observed in a mildly symptomatic individual and in an asymptomatic individual with a score of 0.5 on CDR-SB for judgment. The two asymptomatic cases revealed no change in brain volume. Given that nimodipine did not raise levels of PGRN, we propose this rate of decline may be comparable to untreated GRN mutation carriers. However, we cannot exclude a contribution of volume loss from treatment with nimodipine. If this rate of volume loss is confirmed in a larger cohort of mutation carriers, slowing or reversal of regional gray matter loss could be a viable endpoint in future FTD-GRN clinical trials.
This is the second reported trial to be completed in GRN mutation carriers [7]. There are a number of therapeutic targets in the development pipeline intended for GRN mutation carriers, and this study provides a framework for future bench-to-bedside proof of mechanism studies for FTD-GRN.

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Fig. 1. Nimodipine had no effect on secondary outcome measures in humans, including plasma and CSF PGRN levels and brain volume loss. (A) The mean change in plasma PGRN between baseline (day 0) and the end of the trial (day 56 ± 7) was –1.47 ± 2.1 ng/mL. (B) The mean change in CSF PGRN between baseline (day 0) and the end of the trial (day 56 ± 7) was –0.09 ± 0.04 ng/mL. (C) Elevated neurofilament light chain correlated with disease severity (P = .0002, Mann-Whitney). (D) Elevated tau correlated with disease severity (P = .0002, Mann-Whitney). (E) A significant cluster of gray matter loss was detected in the left middle frontal gyrus (yellow = 20% loss) (cluster extent of 1431 voxels, peak MNI coordinate: –51, 28, 28). (F) The change in brain volume loss was driven by symptomatic mutation carriers.
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Additional contributions: We are grateful to, and offer tremendous thanks to, the participants and their families who made this study possible.

**Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2017.08.002.

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**RESEARCH IN CONTEXT**

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. Heterozygous loss of function mutations in the progranulin gene (GRN) lead to frontotemporal dementia (FTD) through decreased production of the normal progranulin protein (PGRN). Therapeutic approaches have focused on finding novel compounds that increase PGRN levels. In murine model systems, calcium channel blockers were discovered to increase PGRN levels. We launched a phase 1 trial of nimodipine in GRN mutation carriers to test safety and tolerability.

2. Interpretation: Nimodipine was safe and well tolerated but is unlikely to provide therapeutic benefit in GRN FTD.

3. Future directions: This trial demonstrated that a nimble, small-scale trial could arise entirely from, and be contained within, an academic center. From the initial target identification to the execution of human trials, this trial provides a framework for future bench-to-bedside proof of mechanism studies in FTD.

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