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Arimoclomol and levacetylleucine for the treatment of neurologic manifestations of Niemann-Pick disease type C: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Niemann-Pick disease type C (NPC) is an autosomal recessive disorder caused by pathogenic variants in *NPC1* (OMIM 257220, HGNC:7897) or *NPC2* (OMIM 607625, HGNC:14537).[1] Both genes encode lysosomal proteins, the loss of which leads to lysosomal accumulation of unesterified cholesterol and sphingolipids.[2] Clinical presentations are heterogenous and range from in utero to adult-onset symptoms. The infantile-onset form of NPC is characterized by cholestatic liver disease, hepatosplenomegaly, and pulmonary infiltrates, whereas later presentations include

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progressive neurologic symptoms, including cognitive impairment, cerebellar ataxia, psychiatric manifestations, and seizures, in addition to visceral disease.[1] The most common cause of death in individuals with neurological symptoms is aspiration pneumonia preceded by dysphagia.[3]

Management and treatment

Management guidelines for NPC have been published, which include monitoring for organomegaly, mobility, swallowing, hearing, neurocognitive impairments, psychiatric disease, and providing supportive care.[4-6] Before 2024, there were no FDA-approved treatments for NPC. Miglustat, an inhibitor of glucosylceramide synthase, has been approved to treat NPC in other countries; however, its use remains off-label in the United States. Miglustat has been shown to ameliorate neurological symptoms and extend survival but does not arrest disease progression.[7] Current guidelines recommend that miglustat treatment be considered for symptomatic patients without advanced neurologic involvement.[5]

Newly approved therapy

Indications

In September 2024, the FDA approved 2 new drugs for the treatment of the neurological manifestations of NPC: Arimoclomol (MIPLYFFA) in patients 2 years of age and older and Levacetylleucine (AQNEURSA) in patients greater than 15 kg. Arimoclomol approval was conditional upon cotreatment with miglustat.

Mechanisms of action

Neither drug has a fully understood mechanism of action. Arimoclomol is a synthetic pyridine derivative that upregulates heat-shock proteins, in particular HSP70, reducing cellular stress, and improving lysosomal function. In NPC, this may reduce lipid accumulation.[8] Levacetylleucine may improve metabolism-related energy production, normalize neuronal membrane potential, and improve lysosomal function and neuroprotection.[9]

Outcomes and efficacy

The efficacy of arimoclomol was supported by a prospective, randomized, double-anonymized, placebo-controlled phase 2/3 trial in 50 participants (ages 2 to 18 years) stratified by miglustat use (NCT02612129).[10] The primary endpoint was change in disease progression using a 25-point severity scale (NPCCSS) following 12 months of therapy. A statistically significant decrease of 1.40 points was documented in the arimoclomol treatment group, indicating slowed disease progression over the 1-year study.[10] The greatest benefit (decrease of 2.06 points) was seen in participants also receiving miglustat. These findings were presented to the FDA in 2021, and concerns regarding effectiveness were raised.[11] Resubmitted data with a modified severity score (R4DNPCCSS; excluding cognition and re-scoring the swallowing domain) showed a reduction of 2.2 points favoring arimoclomol over placebo with miglustat cotreatment.

The efficacy of levacetylleucine was supported by 2 studies. A phase-2 open-label, rater-anonymized study in 33 participants with NPC aged 7-64 years (NCT03759639) demonstrated improvements in the primary endpoint of a 7-point Clinical Impression of Change in Severity scale during a 6-week treatment period compared with a 6 week washout period (mean difference 0.86, $P = .029$).[12] In a phase-3 crossover trial in 60 participants with NPC ages 4 years or older (NCT05163288),[13] the primary endpoint was the total score on the 40-point Scale for the Assessment and Rating of Ataxia after 12 weeks of levacetylleucine followed by placebo for 12 weeks, and vice versa. Secondary endpoints included scores on the Clinical Global Impression of Improvement, the Spinocerebellar Ataxia Functional Index, and the Modified Disability Rating Scale. In the 59 participants dosed, levacetylleucine treatment was associated with an improvement of 1.28 points (out of 40) on the Scale for the Assessment and Rating of Ataxia after 12 weeks of treatment compared with placebo. Cotreatment with miglustat was reported in 50 of 59 participants. The study did not use validated NPC-related biomarkers.

Neither trial addressed nonneurological manifestations, such as liver disease.

Adverse effects and toxicity

Arimoclomol carries a boxed warning for hypersensitivity reactions, including urticaria and angioedema, embryofetal toxicity, and creatinine elevations (mean 10%-20% increase) due to inhibition of organic cation transporter 2 in the kidneys.[14] In the clinical trial, 78% of participants received miglustat and adverse events occurred in 88% of participants receiving arimoclomol.[10] The most common adverse effect was vomiting, with similar frequency (23%-25%) during arimoclomol and placebo administration. Upper respiratory tract infection and decreased weight occurred more frequently (>5%) during arimoclomol administration. Three participants discontinued arimoclomol treatment after serious adverse events, including hypersensitivity with urticaria and angioedema and elevated creatinine $\geq$2 times the baseline.[10] These adverse effects reversed after arimoclomol discontinuation.

Levacetylleucine carries a boxed warning for embryofetal toxicity, and contraception should be used during treatment and for seven days after the last dose.[15] In NCT03759639,[12] 93.8% of participants also received miglustat. Adverse events/effects occurred in 73% of participants. No adverse events occurred with a frequency of more than 10%; most commonly, rhinitis, seizure, fall, diarrhea and gastroenteritis, upper or lower respiratory tract infections, epistaxis, rash, or pruritis.

Most NPC clinical trial participants in both placebo and treatment arms were also receiving miglustat at unspecified doses and duration. The studies showed similar adverse event rates between treatment and control groups, but the small sample sizes, lack of miglustat usage data, and absence of adverse event stratification by miglustat use prevent definitive conclusions about causality.

In NCT05163288,[13] 85% of participants also received miglustat. Adverse effects were reported in 60% of participants receiving levacetylleucine and 51% receiving placebo. No adverse events occurred with a frequency of more than 10%; most commonly, upper respiratory tract infections, falls, and dysphagia. No adverse effects led to trial withdrawal.

Additional considerations

- Arimoclomol is only approved for co-use with miglustat, and levacetylleucine trials included a majority of participants also treated with miglustat. Thus, the effectiveness of these 2 new treatments in the absence of miglustat remains difficult to interpret. Miglustat for NPC remains off-label in the United States.
- There are no published studies of outcomes or safety addressing coadministration of arimoclomol and levacetylleucine.
- Available data for treatment of NPC with arimoclomol or levacetylleucine beyond 5 years are extremely limited; long-term outcomes are not known.

Conflict of Interest

All workgroup members receive salary for providing clinical services that may be relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations. Irene J. Chang is a principal investigator for unrelated clinical trials sponsored by Denali Therapeutics. All other authors declare no additional conflicts of interest.

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