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EDITORIAL

FDA approval of Miplyffa and Aqneursa: A dual breakthrough for the treatment of Neimann–Pick disease type C

In September 2024, the U.S. Food and Drug Administration (FDA) approved two innovative therapies for Niemann–Pick disease type C (NPC). The first drug, Miplyffa (arimoclomol), received approval on September 20, 2024, for treating NPC in adults and children aged 2 years and older.[1] Within a week, on September 24, 2024, Aqneursa (N-acetyl-L-leucine [NALL]) was also authorized to address neurological symptoms associated with NPC in both adult and pediatric patients weighing at least 15 kg.[2] These approvals represent a groundbreaking advancement in the management of NPC, offering new hope for NPC patients as they are the first drugs to be approved by the FDA.

With approximately 1 in 120,000 live births reported worldwide, NPC is a rare autosomal recessive lysosomal storage disease that results from a mutation in genes of NPC1 or NPC2 proteins. Approximately 95% is due to the NPC1 mutation, and only 5% of pathogenic variants occur in NPC2 proteins. These proteins transport cholesterol from lysosomes and regulate lipid content within membranes. Mutation disrupts normal transport, accumulating cholesterol in various tissues, particularly the liver, spleen, and brain. Its prevalence varies by region and population.[3]

Clinical manifestations of NPC are typically age-dependent. In the early infantile period, patients often exhibit delays in developmental motor milestones along with cognitive impairments. In the juvenile phase, individuals may experience gait problems and difficulties in school. In the adult form, psychiatric disturbances are commonly observed. Further neurological signs can include dysarthria, dysphagia, cerebral ataxia, dementia, and seizures. Visceral issues may involve hepatomegaly, splenomegaly, and cholestatic jaundice. Ocular abnormalities are also prevalent, with vertical supranuclear ophthalmoplegia (VSO) being the most common.[3] In a study of NPC-diagnosed cases, 76% of patients presented with cerebral ataxia, 75% with VSO, 63% with dysarthria, 54% with splenomegaly, and 45% with psychiatric disorders. Despite the variable age of onset, it is essential to note that infantile onset of the disease, particularly with neurological impairment, is associated with a comparatively worse disease progression than juvenile or adult-onset.[4]

There is currently no cure for this disease. However, supportive treatment strategies include both pharmacological and non-pharmacological interventions. The only approved drug for NPC in Europe is miglustat (Zavesca), which inhibits glucosylceramide synthase, thereby reducing lipid accumulation.[5] The drug has yet to be approved by the FDA and only slows down the progression of neurological symptoms. Non-pharmacological approaches, such as speech therapy, physical therapy, and nutritional support, are also important for improving the quality of life in NPC patients.[6,7] Hence, there is a clear need for novel therapy to treat this rare ailment. Another promising treatment involves cyclodextrins, which help extract excess cholesterol from cell membranes.[8] Additionally, Vorinostat, a histone deacetylase inhibitor, has effectively prevented lipid accumulation in lysosomes.[5]

Recently, Arimoclomol and NALL both have gained FDA approval for NPC treatment. Arimoclomol amplifies the activity of heat shock proteins (HSPs), thereby improving lysosomal function and cellular homeostasis. HSPs play an important role in processing NPC1 protein, lysosomal membrane stability, and protection from cell death.[9] On the other hand, NALL is the L-enantiomer of N-acetyl-DL-leucine, administered orally and absorbed by monocarboxylate transporters found throughout the body, including the brain. It enhances Adenosine triphosphate (ATP) energy production by correcting metabolic dysfunction, which improves mitochondrial and lysosomal functions. This normalization of energy metabolism reduces the accumulation of unesterified cholesterol and sphingolipids. Additionally, it appears to reduce neuroinflammation in various animal models, suggesting a potential neuroprotective effect.[10]

The approvals come after positive outcomes seen in the respective trials. Arimoclomol (randomized, double-blind, placebo-controlled, phase 2/3 trial) included a cohort of 50 patients aged 2–18 with genetically confirmed NPC mutations, grouped by their use of miglustat. Then, the patients were randomized in a 2:1 ratio to receive arimoclomol or placebo thrice daily for 12 months. In terms of primary endpoint after 12 months, arimoclomol exhibited a significant change in the five-domain NPCCSS score compared to the placebo group, indicat-

ing a significant therapeutic effect in favor of arimoclomol reflecting a 65% relative decrease in yearly disease progression. The safety profile was consistent with adverse gastrointestinal effects, primarily vomiting. However, upper respiratory tract infections and decreased weight were more prevalent in the arimoclomol group than in the placebo group. Nonetheless, the safety profile was satisfactory.

Similarly, the effectiveness of NALL was studied in a phase 3, randomized, placebo-controlled trial. The study included 60 patients aged 5–67 years stratified in a 1:1 ratio to receive NALL for 12 weeks (85% of the patients were on Miglustat and continued the therapy during the trial). For the primary endpoint, following the 12-week NALL therapy, the mean change from baseline in the total Scale for the Assessment and Rating of Ataxia (SARA) score was significant in the NALL group compared to placebo. Conversely, the 29 patients who started with NALL and switched to placebo experienced worsening symptoms; additionally, their SARA scores increased after stopping NALL, indicating a possible decline in neurological status in the absence of NALL. Moreover, no more than 10% of the patients experienced transient adverse events, including upper respiratory tract infection, anal incontinence, restless legs, and rosacea when they were receiving NALL. However, none of the adverse effects were severe, indicating a satisfactory safety profile.

In conclusion, the FDA approval of arimoclomol and levacetylleucine marks a significant advancement in the treatment of Niemann–Pick disease type C, as they are the first medications to be approved for this condition. These drugs offer much-needed relief for individuals suffering from this rare ailment. However, further research is necessary to comprehend its long-term complications and optimum dosage to administer fully.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the study. All authors approve the final version of the article. All listed authors have made significant intellectual contributions to the conception, design, analysis, and/or interpretation of the work in this manuscript.

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None

CONFLICT OF INTEREST STATEMENT

The Authors declare that they have no financial conflict of interest with regard to the content of this report.

DATA AVAILABILITY STATEMENT

Not applicable as no new dataset was generated during the study.

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REFERENCES

1. Commissioner of the FDA. *Approves First Treatment for Niemann-Pick Disease, Type C*. FDA; 2024. Accessed October 8, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-niemann-pick-disease-type-c
2. Commissioner of the FDA. *Approves New Drug to Treat Niemann-Pick Disease, Type C*. FDA; 2024. Accessed October 8, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treat-niemann-pick-disease-type-c
3. Vanier MT. Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2010;5:16. doi:10.1186/1750-1172-5-16
4. Sévin M, Lesca G, Baumann N, et al. The adult form of Niemann-Pick disease type C. *Brain*. 2007;130(Pt 1):120-133. doi:10.1093/brain/awl260
5. Sitarska D, Tylki-Szymańska A, Ługowska A. Treatment trials in Niemann-Pick type C disease. *Metab Brain Dis*. 2021;36(8):2215-2221. doi:10.1007/s11011-021-00842-0
6. Palmieri M, Cariati I, Scimeca M, et al. Effects of short-term aerobic exercise in a mouse model of Niemann-Pick type C disease on synaptic and muscle plasticity. *Ann Ist Super Sanita*. 2019;55(4):330-337. doi:10.4415/ANN_19_04_05
7. Wheeler S, Sillence DJ. Niemann-Pick type C disease: cellular pathology and pharmacotherapy. *J Neurochem*. 2020;153(6):674-692. doi:10.1111/jnc.14895
8. Höller A, Albrecht U, Baumgartner Sigl S, et al. Successful implementation of classical ketogenic dietary therapy in a patient with Niemann-Pick disease type C. *Mol Genet Metab Rep*. 2021;27:100723. doi:10.1016/j.ymgmr.2021.100723
9. Kirkegaard T, Roth AG, Petersen NH, et al. Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. *Nature*. 2010;463(7280):549-553. doi:10.1038/nature08710
10. Churchill GC, Strupp M, Factor C, et al. Acetylation turns leucine into a drug by membrane transporter switching. *Sci Rep*. 2021;11(1):15812. doi:10.1038/s41598-021-95255-5

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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