Pompe disease ERTs: Are incremental gains enough for your patients?

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Late-onset Pompe disease presents a chronic, debilitating challenge, with progressive muscle weakness and respiratory insufficiency significantly impacting patient quality of life. For two decades, enzyme replacement therapy (ERT) has been the cornerstone of management, but limitations in efficacy and delivery have driven the search for improved options. Now, two next-generation ERTs, avalglucosidase alfa and cipaglucosidase alfa, aim to address these shortcomings, showing enhanced lysosomal targeting and enzyme uptake.

KEY TAKEAWAYS

- The Pivot: Next-generation ERTs, avalglucosidase alfa and cipaglucosidase alfa, offer improved enzyme delivery compared to alglucosidase alfa.
- The Data: Avalglucosidase alfa demonstrated a 2.4-point greater improvement in forced vital capacity (FVC) percent predicted compared to alglucosidase alfa at 49 weeks (95% CI, 0.1-4.7; P=.04).
- The Action: Clinicians should consider these newer ERTs for patients with late-onset Pompe disease, particularly those with suboptimal responses to conventional alglucosidase alfa, while managing expectations for incremental gains.

Pompe disease, a rare autosomal recessive lysosomal storage disorder, results from a deficiency of acid alpha-glucosidase (GAA), leading to glycogen accumulation in various tissues, particularly muscle. The clinical spectrum ranges from rapidly progressive infantile-onset disease to a more slowly progressing late-onset form, which can manifest from childhood to adulthood. For adults with late-onset Pompe disease, progressive myopathy and respiratory failure are the primary concerns, often leading to significant disability and reduced life expectancy.1

Alglucosidase alfa, the first approved ERT, has been available for over two decades, offering a foundational treatment. But its efficacy is often incomplete, particularly in patients with significant muscle damage or those developing anti-drug antibodies. This unmet need spurred the development of newer agents designed for enhanced cellular uptake and lysosomal delivery.1

Comparing the Next-Generation ERTs

Avalglucosidase alfa, approved in 2021, is a recombinant human GAA engineered with an increased mannose-6-phosphate (M6P) content, which facilitates greater uptake into lysosomes via the M6P receptor. This design aims to improve enzyme delivery to target cells, theoretically enhancing glycogen clearance. The study comparing avalglucosidase alfa to alglucosidase alfa in treatment-naive patients with late-onset Pompe disease showed a statistically significant, albeit modest, improvement in respiratory function.1

Patients receiving avalglucosidase alfa demonstrated a 2.4-point greater improvement in forced vital capacity (FVC) percent predicted compared to those on alglucosidase alfa at 49 weeks (95% CI, 0.1-4.7; P=.04). This difference, while statistically significant, represents a relatively small absolute gain for patients. Muscle function, measured by the 6-minute walk test (6MWT), also showed a numerical improvement of 30 meters with avalglucosidase alfa versus 2.4 meters with alglucosidase alfa, but this difference did not reach statistical significance (P=.06).1

Cipaglucosidase alfa, the other next-generation ERT, is part of a two-component system that includes miglustat, an enzyme stabilizer. Cipaglucosidase alfa is a recombinant human GAA, while miglustat acts as a pharmacological chaperone, stabilizing the enzyme and potentially enhancing its activity and half-life within the lysosome. This combination aims to optimize enzyme function and reduce degradation.1

Clinical trials for cipaglucosidase alfa have focused on its efficacy and safety, particularly in patients previously treated with alglucosidase alfa. Data from these studies indicate that cipaglucosidase alfa can maintain or improve respiratory and motor function in patients transitioning from alglucosidase alfa. For example, in one study, patients switching to cipaglucosidase alfa maintained their FVC and 6MWT performance over 52 weeks, with some showing modest improvements.1

Real-World Performance and Practical Considerations

Beyond the controlled environment of clinical trials, real-world data for these newer ERTs are beginning to emerge, offering insights into their performance in broader patient populations. For avalglucosidase alfa, initial real-world observations largely align with trial results, confirming its safety profile and demonstrating sustained, albeit incremental, benefits in respiratory and motor function. Clinicians are finding that the improved M6P targeting translates to better enzyme uptake in some patients, particularly those who may have had a suboptimal response to alglucosidase alfa.1

Still, the transition from alglucosidase alfa to avalglucosidase alfa requires careful monitoring, as individual patient responses can vary. Some patients experience clear benefits, while others see only marginal changes. This variability underscores the complex pathophysiology of Pompe disease and the impact of factors like disease duration, muscle damage, and immune response. For a deeper understanding of how rare disease patients navigate these treatment options, our previous coverage on hurdles beyond diagnosis and treatment offers additional context.

Cipaglucosidase alfa, with its chaperone component, presents a different set of considerations. The co-administration of miglustat adds a layer of complexity to treatment, but the rationale is sound: stabilizing the enzyme within the lysosome could lead to more efficient glycogen degradation. Real-world experience with cipaglucosidase alfa is still accumulating, but early indications suggest it can be a viable option for patients, especially those who might benefit from enhanced enzyme stability. The Oxford Handbook of Neurology provides a concise reference for managing such complex neurological conditions.

Where the Evidence Falls Short

While both avalglucosidase alfa and cipaglucosidase alfa represent advances, neither is a panacea. The improvements observed are generally modest, reflecting the chronic and progressive nature of Pompe disease and the challenges of reversing established muscle damage. The trials were not powered to detect differences in all subgroups, and the long-term durability of these benefits remains an area of ongoing investigation. The impact of anti-drug antibodies, a known issue with alglucosidase alfa, also needs further elucidation with these newer agents.1

Direct head-to-head comparisons between avalglucosidase alfa and cipaglucosidase alfa are lacking, making it difficult to definitively state which offers superior benefits. Clinicians must therefore rely on indirect comparisons and individual patient characteristics when making treatment decisions. The cost-effectiveness of these newer, often more expensive, therapies also warrants consideration in healthcare systems with finite resources. For a broader perspective on similar challenges in other rare genetic disorders, our article on Fabry Disease and enzyme replacement highlights analogous issues.

The open-label design of some studies, particularly those involving switches from alglucosidase alfa, is an obvious caveat. While necessary for rare diseases, it introduces potential for bias. The reliance on surrogate endpoints like FVC and 6MWT, while clinically relevant, may not fully capture the patient's overall functional improvement or quality of life. The field continues to seek more comprehensive outcome measures that reflect the true burden of the disease.1

The long-term impact on bone health, cardiac function, and other systemic manifestations of Pompe disease also requires more extensive follow-up. While the primary focus is often on respiratory and motor function, Pompe disease is a multisystem disorder, and a holistic view of treatment efficacy is essential. This is particularly relevant given the progressive nature of the disease, where subtle changes over time can accumulate into significant clinical impact.1

"The advancements in enzyme replacement therapy for Pompe disease, while incremental, underscore the persistent need for therapies that can not only halt but reverse the debilitating progression of this rare disorder."van der Beek NAME, Curr Opin Neurol 2025The development of these next-generation ERTs marks a step forward in the management of late-onset Pompe disease, but the journey is far from over. Future research will need to focus on optimizing treatment strategies, identifying biomarkers for response, and exploring combination therapies that target different aspects of the disease pathophysiology. The goal remains to provide patients with treatments that offer substantial and sustained clinical benefits, truly transforming their lives.1

CLINICAL IMPLICATIONS

For clinicians managing late-onset Pompe disease, the arrival of avalglucosidase alfa and cipaglucosidase alfa means more options, but also more complexity. These are not revolutionary drugs that will erase the disease, but rather refinements on an established principle. Expect incremental gains in respiratory and motor function, particularly in patients who have not responded optimally to alglucosidase alfa.

The choice between avalglucosidase alfa and cipaglucosidase alfa will likely hinge on individual patient factors and emerging real-world data. Avalglucosidase alfa's enhanced M6P targeting offers a direct mechanism for improved cellular uptake, while cipaglucosidase alfa's chaperone component aims for better enzyme stability. Neither has definitively proven superiority over the other in head-to-head trials, so clinical judgment, informed by the nuances of each patient's disease progression and prior treatment history, will be paramount.

Pay close attention to the practicalities: avalglucosidase alfa is administered every two weeks, similar to alglucosidase alfa, but cipaglucosidase alfa involves a two-component system. This might influence patient adherence and logistical considerations. The cost implications of these newer therapies will undoubtedly factor into access and prescribing decisions across European healthcare systems, requiring careful consideration of the value proposition for the observed benefits.

These new ERTs underscore the ongoing challenge of treating rare, progressive diseases. While they offer a tangible improvement, they also highlight the need for continued research into therapies that can deliver more

> profound and sustained clinical outcomes, perhaps through gene therapies or other novel approaches that address the root cause more effectively.

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REFERENCES

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