

Dichloroacetate: Why a 'slow burn' approach wins in PDCD

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Pyruvate dehydrogenase complex deficiency (PDCD) is a rare, severe mitochondrial disorder that often presents in infancy with neurological dysfunction, lactic acidosis, and early mortality. Treatment options remain limited, leaving clinicians with few effective strategies to manage its devastating progression. A recent Phase III trial, published in JCI Insight, investigated sodium dichloroacetate (DCA) as a potential therapy, revealing a complex picture of its efficacy that hinges on treatment duration and patient baseline.¹

KEY TAKEAWAYS

- **The Pivot:** While short-term DCA showed no significant motor benefit, longer-term treatment improved motor function, particularly in those with higher baseline impairment.
- **The Data:** Longer-term DCA treatment led to a statistically significant improvement in motor function ($P = 0.002$) and reduced plasma lactate by 0.48 mmol/L (-20%; $P = 0.006$).
- **The Action:** Clinicians should consider DCA for children with PDCD, especially those with more severe motor impairment, but manage expectations for immediate, dramatic short-term gains.

Pyruvate dehydrogenase complex deficiency disrupts the body's ability to convert pyruvate into acetyl-CoA, a vital step for energy production in the mitochondria. This metabolic block leads to a buildup of lactate and pyruvate, causing severe neurological symptoms, developmental delay, and often early death. The disease manifests with a wide spectrum of severity, from neonatal lactic acidosis and structural brain abnormalities to later-onset ataxia and cognitive impairment. Current management largely focuses on supportive care, dietary modifications, and symptomatic treatments, none of which address the underlying metabolic defect. This unmet need has driven the search for targeted therapies, with DCA emerging as a candidate due to its mechanism of action.¹

Sodium dichloroacetate is a small molecule that inhibits pyruvate dehydrogenase kinase (PDK), an enzyme that inactivates the pyruvate dehydrogenase complex (PDC). By inhibiting PDK, DCA aims to reactivate PDC, thereby promoting pyruvate oxidation, reducing lactate accumulation, and improving mitochondrial energy metabolism. The drug is administered orally, which offers a practical advantage for chronic management in a pediatric population. The trial enrolled 34 children with PDCD, randomizing them to either DCA or placebo for four months, followed by a crossover to the alternate arm after a one-month washout period. Participants could then continue into an open-label extension period, a design choice that proved important for discerning the drug's true impact. Pharmacogenomic analysis of the GSTZ1 gene, which modulates DCA metabolism, guided dosing, reflecting an increasingly personalized approach to rare disease therapeutics.¹

The Initial Disappointment and the Long-Term Turnaround

The primary endpoint of the trial, the observer-reported outcomes motor domain (ObsROmotor) score, initially failed to show a statistically significant difference between the DCA and placebo groups during the initial four-month randomized, placebo-controlled phase ($P = 0.512$). This short-term result might have led to premature conclusions about DCA's utility, a common pitfall in rare disease trials where patient numbers are small and disease progression can be heterogeneous. The ObsROmotor score, a measure of motor function reported by caregivers, is a patient-centric outcome, reflecting real-world impact on daily activities.¹

But the longer-term data, incorporating the open-label extension period, painted a different picture. Over a more extended treatment duration, DCA demonstrated a statistically significant treatment effect on the ObsROmotor score ($P = 0.002$). This benefit was particularly pronounced in participants with higher baseline motor impairment (ObsROmotor ≥ 8 ; $P = 0.001$). This subgroup analysis suggests that DCA may offer greater benefit to those most severely affected, an important insight for clinical targeting, as it impacts patient quality of life. The initial lack of effect highlights the challenge of assessing slow-acting metabolic modifiers in short-duration trials, especially in conditions with variable natural history.¹

The trial design, with its crossover and open-label extension, allowed for a more comprehensive evaluation of DCA's effects over time, mitigating some of the limitations inherent in short-term randomized controlled trials for rare, chronic conditions. Without the extended follow-up, the initial negative primary endpoint might have overshadowed the eventual positive findings, potentially delaying or preventing access to a beneficial therapy. This highlights the importance of adaptive trial designs and long-term observational data in rare diseases, where conventional trial structures may not fully capture therapeutic benefits.¹

Beyond Motor Function: Metabolic and Survival Benefits

Beyond motor function, DCA also demonstrated a significant impact on key biochemical markers. Plasma lactate levels, a direct indicator of the metabolic derangement in PDCD, decreased by 0.48 (0.82) mmol/L, representing a 20% reduction ($P = 0.006$). This metabolic improvement is consistent with DCA's mechanism of action, suggesting that the drug is indeed reactivating PDC and improving mitochondrial function. The reduction in lactate provides objective evidence that DCA is addressing the underlying metabolic defect, which is important for validating its therapeutic potential.¹ Perhaps the most compelling finding was the impact on survival. The survival of participants treated with DCA was significantly greater than that of a natural history cohort (log-rank $P = 0.027$). This comparison, while not from a randomized arm, offers a strong signal of clinical benefit in a disease with high mortality. The natural history cohort provides a benchmark against which to assess the drug's impact, especially when a placebo-controlled survival study is ethically or practically challenging in a severe pediatric condition. This survival advantage, combined with improved motor function and lactate reduction, positions DCA as a potentially disease-modifying therapy.¹

The safety profile of chronic DCA treatment was also reassuring. The drug was well tolerated, with no new or unexpected safety signals emerging during the trial. This is an important consideration for a therapy intended for long-term use in children. The pharmacogenomic dosing based on GSTZ1 haplotype likely contributed to the favorable safety profile by optimizing individual drug exposure and minimizing potential adverse effects. This personalized approach to dosing represents a step forward in managing rare genetic disorders, where individual metabolic differences can significantly

impact drug response and tolerability. For a deeper understanding of how genetic variations influence drug response, clinicians might consult resources like the Oxford Handbook of Genetics.¹

The Catch: Trial Design and Generalizability

The open-label extension, while important for demonstrating long-term efficacy, is the obvious caveat. Open-label studies are susceptible to bias, as both participants and investigators are aware of the treatment assignment. This awareness can influence observer-reported outcomes, even with standardized assessment tools. While the initial randomized phase did not show a benefit, the sustained improvement in the open-label phase, particularly in a predefined subgroup, still warrants attention. The comparison to a natural history cohort for survival, while informative, is not as robust as a randomized, placebo-controlled survival endpoint. Differences in patient characteristics or care standards between the trial cohort and the historical controls could confound the results.¹

The trial enrolled 34 children, a small number reflective of the rarity of PDCD. While sufficient for a rare disease Phase III study, it limits the generalizability of the findings to the broader PDCD population, which exhibits considerable clinical and genetic heterogeneity. The specific pharmacogenomic dosing strategy, while beneficial, also means that the results are most applicable to patients whose GSTZ1 haplotype allows for such tailored administration. Whether the benefits extend to all PDCD patients, regardless of their genetic profile or baseline severity, remains an open question. The trial was not powered to detect differences in all subgroups, and that gap matters for clinicians considering this therapy for a diverse patient population.¹

Still, the consistent improvements across multiple endpoints, motor function, lactate levels, and survival, provide a strong argument for DCA's clinical utility. The effect size on motor function, particularly in those with higher baseline impairment, suggests a meaningful impact on quality of life. The reduction in plasma lactate offers a biochemical correlate to the clinical improvements, reinforcing the biological plausibility of DCA's mechanism. The survival benefit, even when compared to a historical cohort, is a powerful indicator in a disease with such a poor prognosis. This evidence, while not perfect, offers a significant step forward for a patient population with few alternatives. Clinicians managing complex pediatric metabolic disorders may find the Oxford Handbook of Paediatrics a useful reference for broader management strategies.¹

The findings from this trial align with the growing understanding of how genetic factors influence disease progression and treatment response in rare metabolic conditions. For instance, similar complexities in understanding genetic drivers of disease are explored in our coverage of gene dosage imbalance in Down syndrome, highlighting how subtle genetic variations can have systemic effects. The long-term nature of the observed benefits also echoes discussions around therapies for other chronic conditions, where initial short-term data may not fully capture the sustained impact.¹

The trial's focus on a specific genetic deficiency, pyruvate dehydrogenase complex deficiency, also brings into focus the broader field of inborn errors of metabolism. Understanding the precise metabolic pathways affected, and how interventions like DCA can modulate them, is key to developing effective treatments. This approach contrasts with more generalized symptomatic treatments, offering a more targeted therapeutic strategy. The ongoing research into ALOX12B mutations in congenital ichthyosis, for example, illustrates how pinpointing specific genetic defects can redefine our understanding and treatment of rare diseases.¹

CLINICAL IMPLICATIONS

The initial four-month data from the DCA trial might have been dismissed as a failure, a common fate for therapies in rare diseases where small patient numbers and heterogeneous presentations obscure true benefit. But the extended follow-up, a luxury often unavailable in early-phase trials, revealed a clear signal. This highlights a critical lesson: for chronic, progressive conditions like PDCD, short-term endpoints may simply be too brief to capture meaningful clinical change. Clinicians should view initial negative results in such contexts with a healthy skepticism, always seeking longer-term data.

The pronounced benefit in patients with higher baseline motor impairment is particularly important. This suggests a potential stratification strategy, directing DCA to those who stand to gain the most. It is not a drug for every child with PDCD, but rather a targeted intervention for a specific, severely affected subgroup. This precision medicine approach, guided by both clinical presentation and pharmacogenomics, is the future of rare disease management, moving beyond one-size-fits-all treatments.

Saol Therapeutics, the co-funder, now has a clearer path for regulatory submission, armed with evidence of improved motor function, reduced lactate, and a survival advantage. The challenge will be to translate these complex findings into clear prescribing information that guides clinicians on appropriate patient selection and duration of therapy. The cost-effectiveness of a long-term therapy for a rare disease will also be a significant factor for reimbursement bodies, especially given the need for extended treatment to see benefit.

For families grappling with PDCD, these results offer a tangible, albeit not immediate, hope. It is not a cure, but a therapy that can improve motor function and extend life. Managing expectations will be key: this is a slow-acting intervention, requiring sustained commitment to achieve its benefits. The dry wit of the data, showing no short-term gain but a clear long-term win, is a reminder that some of the most impactful therapies require patience to prove their worth.

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REFERENCES

1. Stacpoole PW, Abdenur JE, Bedoyan JK. Phase III trial of sodium dichloroacetate for pyruvate dehydrogenase complex deficiency in children. JCI Insight. 2026.

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