ACTA MYOL 2024;XLIII:114-115;
doi: 10.36185/2532-1900-637

LETTER TO THE EDITOR

The Epigenetic Rescue of Dystrophin Dysfunction study of givinostat in ambulatory Duchenne muscular dystrophy patients

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Dear Editor,

on the April 2024 issue of *The Lancet Neurology*, Mercuri E. and colleagues have published the results of the clinical trial named Epigenetic Rescue of Dystrophin Dysfunction (EPIDYS), which tested the efficacy and safety of the histone deacetylase (HDAC) inhibitor drug givinostat in ambulatory male patients affected with Duchenne muscular dystrophy (DMD) [1]. Givinostat emerges from the EPIDYS study as a novel effective drug for Duchenne muscular dystrophy (DMD), as the authors report significant slowing of the progression of muscle weakness in treated ambulatory DMD patients.

This encouraging result is based on two foundations: the rigorous scientific background of the program in its preclinical stages, and the meticulous study design, which took advantage of the growing knowledge about DMD outcome measures and their modification over time, emphasizing the importance of "natural history" data collected over the last decades.

The potential for histone deacetylase (HDAC) inhibitors to alleviate the inflammatory microenvironment of dystrophic muscle is supported by vast evidence of HDAC hyperactivation in this context, with subsequent reduction of NO signaling and hyperactivation of fibroadipogenic progenitors (FAPs). The inhibition of HDACs modulates the transcriptional programs in myofibers and inflammatory cells, leading to a cascade of beneficial effects, which include an increase in expression of the myostatin inhibitor follistatin, a reduction of fibrosis and fat infiltration, an enhancement of muscle fiber regeneration, reduction in inflammatory infiltrate, and decrease in membrane permeability, demonstrated initially in the *mdx* model [2]. These findings paved the way for the seminal, proof-of-concept phase I-II study in DMD [3], where the primary endpoint was to reproduce the pharmacodynamic effect of givinostat in the muscle tissue analyzed through morphometric analyses of muscle biopsies; clinical outcomes were only included as secondary outcomes in this open-label study.

The EPIDYS study of Givinostat is the first and only phase 3 clinical trial of a non-steroidal drug treatment for DMD, to reach a statistically significant primary outcome. The main strengths of the study design were inclusion criteria, which successfully identified a functionally declining ambulatory population, and the choice of primary and secondary outcomes that are specifically sensitive at the targeted disease stage. Ambulatory DMD

Received: September 12, 2024
Accepted: September 18, 2024

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How to cite this article: Bello L, Sansone V, Masson R, Bruno C. The Epigenetic Rescue of Dystrophin Dysfunction study of givinostat in ambulatory Duchenne muscular dystrophy patients. Acta Myol 2024;43:114-115 https://doi.org/10.36185/2532-1900-637

participants were included not only based on age (≥ 6 years), thus excluding younger boys who may be on an ascending functional trajectory; but also on functional status, defined by upper and lower limits in timed tests such as climbing 4 standard stairs and rising from supine, which predict both short-term [4] and long-term [5] disease progression. Importantly, the timed 4-stair climb was chosen as primary outcome and proved to be a sensitive measure of disease progression for this specific population. Mean treatment-related difference in stair climb velocity loss (1.7 s) is very similar to the minimally clinically relevant threshold identified for the scale, meaning that most of the treated patients experienced a clinically meaningful benefit.

Thanks to an active collaboration with the Imaging-DMD (iDMD) network, the investigators were able to provide evidence, through magnetic resonance spectroscopy (MRS) in a subset of patients, of reduced fat fraction of the vastus lateralis muscle, a crucial predictor of ambulatory function, in treated patients. This finding links the clinical results with one of postulated molecular mechanism, i.e. the downregulation of fibroadipogenesis.

The safety profile, despite some instances of platelet reduction and gastrointestinal issues, seemed manageable. The study design implemented a flexible dose regimen that allowed to reduce drug exposure in case of side effects, and eventually the starting dose was reduced by a protocol amendment; however, analyses of covariance (ANCOVA) showed that dose reduction did not hamper efficacy. Long-term safety data are awaited.

As Givinostat has been recently approved by the Food and Drug Agency, and awaiting European Medicinal Agency approval, the opportunity to add a new therapeutic tool to those available to treat DMD patients will come with some challenges. The precise label that regulators will assign is not well determined as this letter is being drafted, and criteria for patient selection will have to be devised by the community, to prioritize the access to Givinostat based on individual patient features.

In conclusion, the story of givinostat development exemplifies successful translation of mechanistic research, to drug candidate identification, and in turn, through careful and well-informed trial design, to an opportunity of improving DMD care.

Acknowledgements

Medical writing performed by LB and supported by Italfarmaco SpA. Courtesy review has been performed by Italfarmaco SpA for scientific accuracy

Conflict of interest statement

L.B.: consulting fees and/or speaker honoraria from Italfarmaco (also related to the present work), PTC Therapeutics, Sarepta Therapeutics, Roche, Pfizer, Edgewise Therapeutics, UCB (not related to the present work); research grants to the Institution from PTC Therapeutics, Edgewise Therapeutics. V.S.: educational activites and scientific consultant with honoraria in Advisory Boards for Biogen, Roche Novartis, Dyne, PTC, Arthex, Italfarmaco. R.M.: consulting fees and/or speaker honoraria from PTC Therapeutics, Roche, Pfizer, Biogen, Novartis (not related to the present work). C.B. consulting fees and/or speaker honoraria from Roche, Biogen, Novartis (not related to the present work).

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