An update on potential adjuvant therapies in collagen-VI muscular dystrophy (Col6-CMD): Alisporivir, Givinostat and Omigapil

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Summary

In recent years, news have emerged from time to time that point to the potential benefit of some drugs for congenital muscular dystrophy patients. Although they do not hope to cure the disease, these drugs do seek to alleviate the harmful effects that a dysfunctional collagen matrix causes on muscle cells, slowly promoting their destruction. This is the case of alisporivir or givinostat which, like omigapil, have been frequently mentioned in publications and have been the object of both preclinical studies and clinical trials. In this article we summarize what is known about these products, their potential applicability in patients with collagen-VI muscular dystrophy and the current state of their clinical development.

Omigapil

Omigapil is an inhibitor of GAPDH, one of the main mediators of apoptosis –the natural process of cell destruction– which is abnormally exacerbated in the muscle cells of these patients, causing progressive muscle deterioration.

Omigapil was initially developed by Novartis for the treatment of Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALE). Although its use in these two diseases was disregarded due to lack of efficacy, Santhera Pharmaceuticals bought the compound to develop it for the treatment of congenital muscular dystrophy (without specifying a particular pathology). In May 2008, omigapil obtained the designation of orphan drug, which allowed the initiation of clinical studies in these rare diseases.

Thanks to the trials for Parkinson's and ALE, omigapil has been shown to be a drug safe for use in humans and that has no serious noteworthy side effects. As for its potential use in muscular dystrophy, there is preclinical data suggesting that it may improve the symptomatology in these patients, as it could help restore the balance between destruction of muscle tissue (which happens due to exacerbated apoptosis) and its regeneration.

In this sense, treatment of a mouse model of alpha-laminine congenital muscular dystrophy (MDC1A) showed a positive response to omigapil, with inhibition of apoptosis in the muscle, reduction of body weight loss and skeletal deformation, an increase in locomotor activity and a prevention of early mortality.

Following this promising data, the Callisto studio was initiated in December 2014. [1] This study was aimed at establishing the dose of the product in children and adolescents. On the basis of that, the plan was to design a new clinical trial to determine the effectiveness of omigapil in the treatment of due to merosine-deficient and collagen-VI congenital muscular dystrophies, two rare diseases considered to be susceptible to treatment with this drug.

The study was successfully completed in 2018 and the appropriate dose was established. Also, results showed that the product is safe and well tolerated. The short duration of the study, however, did not allow to determine

[1] https://www.clinicaltrials.gov/ct2/show/NCT01805024

the possible therapeutic effect of the treatment in either group of patients (merosine-deficient and collagen-VI).

Based on the information available, the next step in this research project should include two key issues: (i) obtain additional data on the dose-effect relation in animal models and further preclinical data in a Col6-DMC mouse model; and (ii) identify biomarkers to accurately assess the effect of the product without relying solely on functional tests (e.g., 6-minute walk). [2]

To date, however, there are no news about the progress of the project, and Santhera's website has not released any news regarding the development of omigapil in Col6-CMD ever since the completion of the Callisto study in 2018.[3]

Alisporivir

Alisporivir (Debio 025) is a cyclophylin inhibitor (a new category of antiviral agents) with powerful activity against hepatitis C virus. It is currently being developed for the treatment of hepatitis C by Debiopharm and Novartis, as well as for the treatment of SARS-Cov2 (COVID).

However, a preclinical study was published in 2009 showing that this drug can normalize muscle apoptosis and structural defects in a collagen 6 congenital muscular dystrophy.[4] Indeed, the crucial role played by mitochondria in the apoptosis process is common knowledge today, so a product that can correct this dysfunction may offer a therapeutic option for patients with muscular dystrophy, in general.[5]

For this reason, in 2015, Debiopharm (the originator of the drug) together with another pharmaceutical company, Solid Biosciences (dedicated to product development for Duchenne), decided to initiate a collaboration to explore the use of alisporivir in muscular dystrophy, specifically, in Duchenne muscular dystrophy (DMD)[6]. Still, given its mechanism of action is not specific to this pathology, the results can be easily extrapolated to Col6-CMD.

New data subsequently obtained in animal models of muscular dystrophy seem to confirm the positive effect of alisporivir on the recovery of metabolism and structure of muscle cells.[7]

Currently, however, Debiopharm indicates on its website that alisporivir is only under development for the treatment of COVID and gastrointestinal indications (hepatitis C), with no reference to ongoing studies for DMD[8]. Solid Biosciences, although it shows a clear orientation to DMD. Also, Solid Biosciences does not mention alisporivir in its product pipeline[9], suggesting that the collaboration initiated in 2015 may have not yielded sufficient results for the project to progress to a clinical phase.

No published data on the results of these trials has been found.

Givinostat

Givinostat (ITF2357) is a histone deacetylase inhibitor with possible anti-inflammatory, anti-angiogenic and antineoplastic activity.

Specifically, it is an inhibitor of HDAC (histone deacetylase). This is an enzyme involved in gene expression control. It acts in balance with other enzymes, histone acetyltransferases (or HAT), as an activation-

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[2] Oral communication. CURE-CMD Scientific & Family Conference 2019, Chicago, IL (USA)

[3] http://www.santhera.com/

[4] The cyclophilin inhibitor Debio 025 normalizes mitochondrial function, muscle apoptosis and ultrastructural defects in Col6a1 - / - myopathic mice. July 2009. British Journal of Pharmacology 157(6):1045-52

[5] Forty years later: Mitochondria as therapeutic targets in muscle diseases. Alessandra Zulian, Marco Schiavone, Valentina Giorgio, Paolo Bernardi. Pharmacological Research, Volume 113, Part A, 2016, Pages 563-573

[6] Debiopharm press release Sep 2015 ; https://www.debiopharm.com/drug-development/press-releases/debiopharm-international-sa-and-solid-biosciences-llc-announce-a-collaboration-to-explore-the-use-of-alisporivir-debio-025-in-muscular-dystrophy/

[7] Schiavone M, Zulian A, Menazza S, Petronilli V, Argenton F, Merlini L, Sabatelli P, Bernardi P. Alisporivir rescues defective mitochondrial respiration in Duchenne muscular dystrophy. Pharmacol Res. 2017 Nov;125(Pt B):122-131.

[8] https://www.debiopharm.com/drug-development/pipeline/

[9] https://www.solidbio.com/research-development/pipeline-programs/pipeline/

deactivation system for the expression of certain genes. That is, when HDAMs are very active, histones attached to DNA are highly acetylated, DNA will then be transcriptionally active and genes will be expressed. In contrast, when HATs are very active, histones are de-acetylated, DNA is in a very compacted state and gene expression is blocked.

The product was initially developed by the Italian company Italfarmaco, which patented it in 1997 and first described it in the literature in 2005.

Several clinical studies with givinostat are currently underway, including some phase II trials for the treatment of various cancers (such as leukemia or myeloma). In addition, after the product received the designation of orphan drug in the European Union for the treatment of certain rare diseases, a phase III study was initiated to evaluate its use in the treatment of Duchenne muscular dystrophy.

It is known that, in Duchenne, when HDAPs are very active, they contribute to the deterioration of muscle tissue regeneration, since the expression of certain genes such as folistatin, which play a key role in the regenerative process, is reduced or blocked.

In coherence, HDAC inhibitors have been shown to stimulate muscle formation *in vitro* and, therefore, counter muscle degeneration. Also, data from a givinostat activity in a mouse model of Duchenne muscular dystrophy (mdx mice), show that these products promote the expression of a number of factors, including folistatin. Additionally, givinostat possesses a powerful anti-inflammatory effect, so it is expected that the combination of both effects will restore the balance of the muscle destruction-repair process in Duchenne patients towards an increase in muscle regeneration and a reduction of fat infiltration and fibrosis.

In view of this data, in 2017, Italfarmaco initiated a Phase III clinical study with the aim of determining whether givinostat can slow the progression of the disease in children with Duchenne, while, at the same time, assessing the safety and tolerability of the drug.[10] The key data of this study are:

- Title: Randomized, double-blind, placebo controlled, multicenter study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne muscular dystrophy
- Study population: ambulant children, between 6 and 17 years of age.
- Treatment: oral givinostat (10 mg/ml), twice daily,
- Evaluation of the results: The main variable on the basis of which the effect will be determined is the improvement in the 4 standard stairs climb test after 18 months of treatment. In addition, other muscle functional tests will be performed after the same treatment period and taken into account as secondary variables

The trial is currently ongoing, having completed the recruitment phase with a total of 169 patients, and the first results are expected to be available in March 2022.

[10] https://www.clinicaltrials.gov/ct2/show/NCT02851797/