Doctopic: Analysis and Interpretation
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Tamoxifen in children with Duchenne muscular dystrophy

Duchenne muscular dystrophy is a severe neuromuscular condition that affects about one in 5000 male newborn babies.[1] In June, 2023, the US Food and Drug Administration conditionally approved gene therapy with adeno-associated virus microdystrophin for boys aged 4–5 years; the phase 3 trial is ongoing.[2] Despite this major milestone, treatments for boys with Duchenne muscular dystrophy are urgently needed. Furthermore, the magnitude and duration of effect of gene therapy, and the optimal age at which to deliver it, are uncertain. Moreover, with a current price of about US$3 300 000, this genetic treatment is unlikely to be equally available worldwide.

Medications that are inexpensive and that could be used throughout life need to be developed for people with Duchenne muscular dystrophy. These drugs could complement gene therapy, if it is permanently approved. A promising example was tamoxifen, which is a selective oestrogen receptor regulator that is approved for other clinical uses, well tolerated, and inexpensive. This drug had a positive effect in a Duchenne muscular dystrophy mouse model through inhibition of fibrosis and apoptosis and Ca^{2+} homoeostasis regulation.[3] An open-label phase 1 trial showed a good safety profile in children with Duchenne muscular dystrophy.[4] Comparing participants who were treated with tamoxifen with historical controls suggested that tamoxifen preserved motor function, eliciting hope in the Duchenne muscular dystrophy community and resulting in a large investigator-initiated phase 3 trial, for which the results are now reported by Bettina C Henzi and colleagues in *The Lancet Neurology*.[5] Safety and tolerability are confirmed, but efficacy has not been shown. There was no significant difference in the change from baseline to week 48 in scores on the D1 domain of the Motor Function Measure between the tamoxifen group and the placebo group (2·90 percentage points, 95% CI −3·02 to 8·82; p=0·33). The authors investigated potential biases and concluded that only an absence of efficacy could account for the negative results.

Despite this disappointing result, two positive conclusions can be taken from this trial. First, academic investigators, supported by a broad community, were able to fund and conduct a large international trial to investigate the effect of a drug with no potential for financial gain. This trial is a massive endeavour, and the effort should be acknowledged. Second, Henzi and colleagues[5] report these negative results. The reporting of trials with negative findings is of utmost importance. Over the past 15 years, several promising results from phase 1 and phase 2 trials could not be reproduced in double-blind, placebo-controlled studies.[6] The trials investigating the antisense oligonucleotide drisapersen, the coenzyme Q-derived idebenone, and the nuclear factor κ-light-chain-enhancer of activated B cells inhibitor edasalonexent are examples.[6] Blaming clinical trial design or clinical outcome for negative results in phase 3 trials ignores that no outcome measure or clinical trial design will make a non-efficacious drug efficacious.

An additional takeaway from the tamoxifen investigation is that the management of expectations generated by phase 1 trials and the objective interpretation of early efficacy signals are a collective responsibility. Indeed, investigators and sponsors should be cautious when claiming efficacy on the basis of short, open-label, uncontrolled phase 1 trials. Authors and editors should temper the enthusiastic presentation of data from these early-phase trials. Investigators and sponsors should work with the patient community to avoid false claims in social media that overstate the benefits of a drug. Accurate and balanced interpretation of early findings is key for patients and their families, because misinterpretations have led to unnecessary family relocation and crowdfunding for treatments for other diseases, such as spinal muscular atrophy.[7]

Conducting large-scale clinical trials consumes human and financial resources that could be allocated elsewhere. To avoid conducting large phase 3 trials with little chance of showing efficacy, early-phase trials should be properly designed to capture efficacy signals as objectively as possible, and to control for bias. The good news is that the neuromuscular field has developed several strategies that could make early-phase trials more robust: the use of matched external controls,[8] an understanding of independent factors that drive disease evolution,[9] the use of Bayesian design,[9] and digital outcome measures through wearable

technology.[10]

The negative result for tamoxifen in the phase 3 trial should not discourage the community from continuing the evaluation of inexpensive repositioned drugs that have the potential to treat individuals worldwide. It is important to keep in mind that the only drugs that unambiguously work so far for individuals with Duchenne muscular dystrophy are corticosteroids. As potential therapies are identified, robust design, conduct, interpretation, and evaluation of the early-phase trials should be prioritised to optimise the use of resources in the final stages of clinical evaluation.

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