



Current concerns in the therapy of neuromuscular disorders

The risks of therapeutic misconception and $n = 1$ “trials” in rare diseases such as Duchenne dystrophy

1. Introduction

There is currently no cure for Duchenne muscular dystrophy, but there are some promising treatments in development, of which antisense-mediated exon skipping is closest to clinical application. The results of the first trials have resulted in significant enthusiasm among clinicians, patients, and their parents and attracted widespread attention in both the scientific and lay press. As in many other rare diseases with significant morbidity this fuels the hope that at last an effective therapy might be within our reach. Parents, but also some clinicians, are now seriously considering treating individual patients with antisense oligonucleotides without waiting for proof from well-designed clinical trials that the new therapies are indeed effective and safe.

We understand the sense of urgency that is experienced by patients, parents and their clinicians, but we hope to explain that the preliminary introduction of incompletely tested drugs might lead to dangerous and harmful situations for the patients, endanger the continuation of the development of possible effective therapeutic strategies, or even lead to a complete stop in the further development of promising drugs.

2. Exon skipping

The aim of the exon skipping approach is to restore the disrupted dystrophin reading frame to allow the production of Becker-like proteins and potential conversion of the severe Duchenne into the milder Becker muscular dystrophy [1]. Exon skipping is achieved using antisense oligonucleotides, pieces of modified RNA or DNA, which hybridize to a target exon, hide it from the splicing machinery, causing the targeted exon to be “skipped”. A disadvantage of exon skipping is its mutation specificity, as different mutations require the skipping of different exons to restore the open reading frame [2]. As there is a mutation hotspot, skipping some exons applies to larger groups of patients, but even the most applicable exon (exon 51) would benefit only 13% of Duchenne patients [2]. Early phase clinical trials for exon 51 skipping show encouraging results [1] and

trials on exon 44 skipping (applicable to approximately 6% of patients) are currently ongoing. Using two different chemistries exon 51 skipping and dystrophin restoration could be achieved after systemic administration. However, placebo-controlled trials to confirm that longer term treatment is effective and safe have not yet been performed. Nevertheless, requests are made to clinicians for the treatment of individual patients with antisense oligonucleotides targeting exon 51, and also additional exons.

3. The risks of $n = 1$ trials

There is currently no proof that long term treatment with antisense oligonucleotides to induce exon skipping is effective and safe. Functional efficacy (beneficial effects on muscle performance typically assessed by tests such as the 6 min walk test) can only be ascertained with placebo-controlled trials. There are many psychological effects that play a role in trials with children that make controlled trials important [3]. In the early phase trials without a placebo, patients know they are treated with a potential drug. However, there is probably an additional effect, as the children realize their parents know they are treated, and yearn for them to get better. There are examples where there seemed to be a functional effect in early phase trials, which could not be confirmed in a placebo-controlled trial. Of course we all hope there really will be a functional effect after exon skipping treatment, but there is no proof yet. More importantly, placebo-controlled trials are also done to confirm safety of the treatment with antisense oligonucleotides. As antisense oligonucleotides are primarily developed for more acute diseases, not much is known about longer term tolerability and toxicity of these compounds, especially in children and adolescents. Furthermore, the metabolism of Duchenne patients is already compromised (most patients have elevated muscle enzymes, which are occasionally confused with elevated liver enzymes and liver problems), making it very difficult to monitor safety without a placebo group. In conclusion, at this point in time, we do not know yet whether prolonged antisense oligonucleotide treatment is safe in Duchenne patients.

Until efficacy and safety are confirmed, it is arguably unethical to treat patients outside of a controlled trial setting. The optimal dose and dosing regime have not yet been identified and trials have thus far mainly been done in young boys – it is possible that dosing will be different in older boys/men who have less muscle. These boys/men have a severe, progressive disease and without a placebo group it is impossible to conclude that putative negative effects are due to the disease, due to the treatment, due to a combination of the two, or due to an entirely different combination of factors.

$n = 1$ Trials have been done to test drugs in other diseases [4]. Here, the patient is his/her own control and different drugs or a placebo are given over time. This will only work in diseases that are very slowly progressive or episodic. In a more progressive disease like Duchenne muscular dystrophy, patients will not be back to the baseline state when drug treatment is stopped or switched after a number of months. However, the individualized trials as they are requested for Duchenne patients will not compare different compounds in one patient, but rather only a single compound for an indefinite amount of time. As such, these $n = 1$ trials are not trials in the correct sense of the word. Rather they are the administration of potentially harmful substances to a patient in the (possibly unjustified) hope that it might help, but without evidence that there are reasonable chances that it will.

Nevertheless, clinicians/scientists are under a lot of pressure from parents to start these individual “trials”. Scientists may be persuaded to acquiesce, but giving in creates as serious risk of setting the entire field back should anything go wrong. This would extend to the future possibilities for the specific child in the $n = 1$ trial. Clearly with Duchenne being a progressive disease, time is of the essence. However, this does not make it all right to start treatment with any compound before it is confirmed to be safe and effective. For the same reasons, parent and patients cannot invoke “compassionate use” to receive treatment with antisense oligonucleotides, as no conclusive proof has been obtained yet that the treatment will work at longer term with acceptable safety. Even if the individual boys/men agree and accept the risks involved for themselves, the whole field will be set back should something go wrong. This means that if single patients say they accept the risks involved in doing individualized “trials”, both the clinicians and patients involved in these trials accept the risk of delaying (or in the worst case even stopping) the development of a potential treatment for all patients worldwide. For example, young men with Duchenne are at risk from sudden cardiac death. If such an unfortunate event were to occur in a single patient “trial” it would be impossible to know whether the drug might have contributed to this and it might cause alarm for the rest of the field. Experimental drugs used in trials have to undergo extensive testing and regulatory review to ensure adequate quality standards are met before being given to human subjects. In addition, regulatory authorities and ethics committees need to be reassured that adequate monitoring procedures are in place before trials

can start. Increasingly this means the use of an independent monitoring board to regularly review the ongoing safety of the subject in context of the whole trial. These measures help to ensure the safety of trial subjects.

We realize clinicians considering these trials are passionate about helping patients. We want to stress though, that treating patients with something that might not be effective or safe is not “helping” patients.

4. Therapeutic misconception

The requests for exon skipping treatment for individual patients arise from therapeutic misconception. Parents and clinicians considering these “trials” think sufficient evidence has accumulated to support the treatment of their sons or patients without further testing. Unfortunately, this is not the case. Data on new therapeutic approaches and clinical trials should be seen in the right context. However, due to the need to obtain funding and publish results in an increasingly competitive environment, regrettably the terminology used by scientists in the field of applied science tends to oversell findings in cell and animal models in scientific journals and conferences [5]. While their fellow researchers are generally aware of the limitations of the experimental approaches used, this may be more difficult for patients and their families. We should realize that in current times, the patient/parent community of rare diseases is well informed and publications about orphan drugs currently being developed are read by all. Therefore, the entire field (researchers, clinicians and patient advocacy groups) should take responsibility to prevent raising false hope and unrealistic expectations. Obviously, by agreeing to conduct trials in single patients, clinicians only increase misconception and also – should exon skipping fail to work as hoped – increase the sense of loss and disappointment.

We should all realize it is important, especially when interacting with patients and parents to stress the limitations of studies done in cell models (very easy to treat cells, only a proof of concept), animal models (we are not mice – or dogs – and mice have a different disease than humans) and early phase clinical trials (no placebo group). There is a significant gap between studies done in model systems and studies done in patients, and also between early phase clinical trials and placebo-controlled trials. It is also important to communicate more clearly about what exon skipping hopefully can do (slow down disease progression) and what it may not be able to do (bring back lost muscle function). In this, word choice is extremely important. Using words like “medicine”, “cure” or “treatment” based on experiments done in cells or animals, can aberrantly give people the impression there is a real medicine rather than an “experimental drug compound”.

We should also realize that many patients and parents perceive a clinical trial as a form of treatment, rather than an experiment done in humans to test whether a potential drug is effective and safe. Indeed, at times this is even unknowingly stimulated by the caution of approval bodies, who in some

countries allow testing in minors only when a therapeutic effect is expected. Nevertheless, there is a possibility that the tested compound is not effective or safe, and until this has been assessed in a placebo-controlled trial, one should not treat patients outside the trial setting with this compound.

5. The problem of personalized medicine and individualized drug development

The exon skipping approach applies to only subsets of patients and the current development focuses on those exons that would benefit larger groups of patients. In theory exon skipping could be applicable to up to 80% of all patients, but this would require the development of antisense oligonucleotides for over 50 different exons. A dialogue with regulatory agencies to facilitate the development of additional antisense oligonucleotides has been initiated [6]. Antisense oligonucleotides of the same chemistry may eventually be seen as a class, which would facilitate access to new antisense oligonucleotides considerably. Still, some tests to optimize the antisense oligonucleotides and assess their safety will have to be done. More importantly, before considering this as an option, regulatory agencies need confirmation for two or more exon skipping compounds (with the same backbone) that they are safe, effective and act in a similar manner (pharmacokinetic and pharmacodynamic properties) [6]. There are requests to develop antisense oligonucleotides to be tested in individualized “trials”. However, it will take at least 2–3 years to conduct the pivotal studies for exon 51 skipping, which are currently being planned. Therefore it is too early for trials of antisense oligonucleotides applicable to smaller groups of patients. What one should also realize is that these trials (should they ever take place) will involve small groups of patients and not single patients. Finally, aside from the safety and ethical aspects and the risks involved, clinicians considering “treatment” of single patients outside a trial setting should be aware of the practical aspects. Acquiring enough of the compound (antisense oligonucleotides in this case) at a clinical grade will be expensive, especially taking into account that patients will need lifelong treatment.

In summary, we understand the urgency of patients, parents and their clinicians, but hope we too have explained that the whole field benefits only from well conducted trials to confirm safety and efficacy and that individual trials with drugs for which we have insufficient data on safety and efficacy should not be done.

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