



Muscle Meeting

Effects of long-term treatment and combination therapeutics for neuromuscular disorders

Report of a TREAT-NMD/NIH “Bringing down the Barriers – Translational Medicine in Inherited Neuromuscular Diseases” Conference Working Group

1. Introduction

As the medical community is engaging in more novel drug/biologic development and clinical testing for therapies for inherited neuromuscular disorders, new paradigms for decisions making in therapy development are being explored. A concerted effort is needed between the relevant stakeholders to share information, optimize efforts, minimize repeat of the same mistakes, and thereby move novel therapies along more quickly. In addition, multiple therapeutic approaches are now in, or approaching, clinical trials, all competing for a limited number of patients and requiring a clear way forward to understand the spectrum of safety and side effects. Thus, a coordinated approach towards clinical trial development and conduct is crucial. Here, we present a strategy to facilitate long term therapeutic trials for neuromuscular disorders, for monitoring of potential side effects and avoiding pitfalls.

Inherited neuromuscular disorders are an important cause of disability in man. However, there are over a hundred different diseases, which are caused by mutations in different (parts of) genes (see the gene table of Neuromuscular Disorders at www.musclegenetable.org). Even the most common ones (Duchenne muscular dystrophy, myotonic dystrophy, spinal muscular atrophy) are relatively rare diseases when compared to acquired conditions. It has been over two decades since the first genes involved in inherited neuromuscular disorders were reported [1]. However, the advancement from molecular mechanisms to drugs entering clinical trials has been initiated only recently and only for a subset of these disorders [2]. The majority of drugs currently in trials aim to slow down disease progression and address the progressive pathology rather than correcting the underlying genetic defect. However, since many of these genetic neuromuscular diseases can be identified before the development of weakness, the arrest of the disease would be tantamount to cure. Thus, perhaps a realistic goal for the next decade would be that of slowing down or arresting disease progression in several

conditions rather than aiming to improve the condition of affected individuals especially if already significantly compromised. Notably, for only a single disorder (Pompe disease) has a drug been registered that does treat the underlying defect by replacing the α -glucosidase enzyme (myozyme[®]), which normally is lacking in these patients [3]. In this disease treatment appears to arrest the disease in at least some patients [4–6].

Since in most neuromuscular disorder cases life-long treatment will be required, treatments that do not improve function but only slow disease progression pose challenges for clinical development. Complicating this is the lack of data on natural disease course for many NMDs, which impedes assessment of short and long term benefit (or detriment) of treatment. Thus, a consolidated approach to set up clinical trials with an eye to long term surveillance is crucial to advance the development of treatments for these diseases.

2. Long-term treatment goals and outcome measures

Most neuromuscular disorders are progressive diseases, so while treatments that improve muscle function or quality are obviously preferred, patient advocates emphasize that treatments that slow down or stop disease progression would be appreciated as beneficial as well. The latter require long term follow up to assess “benefit”, i.e. a slower disease progression for treated patients than for patients that do not receive the treatment. Even for the commoner and more rapidly progressive diseases such as DMD there is a significant variability in natural history. While part of this relates to differences in biological background of the individuals, part reflects differences in clinical care and management approaches, therefore also highlighting the need for standardization of baseline care to prevent results from being confounded by variable supportive care. TREAT-NMD has been collaborating with other stakeholders in this area to develop and disseminate international guidelines [7–9] (patient friendly translations are available on www.treat-nmd.eu).

A major complicating factor in e.g. Duchenne muscular dystrophy is that the majority of patients are treated with corticosteroids, thus far the only treatment that slows disease progression [10]. Many patient advocacy groups

and clinicians therefore consider it unethical to require patients to stop taking corticosteroids during clinical trials testing other drugs (unless a toxic interaction between the two drugs is anticipated). However, corticosteroid treatment is by no means standardized and 30 different treatment regimes are in use worldwide [11]. There is equipoise concerning the agent (prednisone or deflazacort are used most), the dose, the dosing schedule, the age of initiation, how dosing is modified (e.g. when side effects occur or when patients grow older), and whether treatment should be discontinued. There is also equipoise about side effects: what is the optimal dose to prevent side effects? At what point do the side effects outweigh the benefits of treatment? How can side effects be prevented? Finally, many patients never receive corticosteroid treatment. Clearly the different regimes will alter the progression of the disease when multicenter trials are conducted, both with regards to beneficial effects and side effects. Specifying a single treatment regimen would result in a more consistent rate of progression.

While trials confirm that corticosteroids delay disease progression, few trials compare different corticosteroids

or different dosing regimes [10]. Thus, it is currently impossible to select an optimal dosing regime. In order to allow standardization, a large NIH-funded trial involving 300 DMD patients will soon be initiated where the three most commonly used steroids (0.9 mg/kg deflazacort and 0.75 mg/kg prednisone) and dosing regimes (continuous treatment vs 10 days on and 10 days off) will be compared (FOR-DMD, see <http://www.treat-nmd.eu/about/news/news/836/>). The primary outcome measure is a composite: forced vital capacity, time to rise from the floor and patient satisfaction with the treatment and its side effects. The initial trial will be for 3–5 years, with a planned 10 year follow up. It is hoped that this trial will lead to standardization of steroid treatment and side effect management.

3. Monitoring of long term side effects of (combinations) of treatments

Many treatments are being considered for or tested in clinical trials for Duchenne muscular dystrophy [2] (Table 1). For drug registration, clinical trials rarely last more than 12 or exceptionally 24 months. Most therapies for

Table 1
Adverse effects of experimental drugs for NMD.

A. Restoration of functional dystrophin (or a substitute)		
1. Gene based strategy	Adverse events	Interactions
(A) Gene transfer of dystrophin cDNA (plasmids and high pressure muscle perfusion) or shortened dystrophin cDNA (mini- or microgenes included in AAV or lentivirus)	<ul style="list-style-type: none"> • Immunological reactions, inflammatory reactions, neoplasms • Insertion mutagenesis • Depending on choice of promoter, gene expression in tissues/cells not physiologically expressing it 	Likely necessity to immunosuppress long term
(B) Gene repair (surgery of the gene at the genomic level)	<ul style="list-style-type: none"> • Immunological reactions, inflammatory reactions, neoplasms? • Induction of mutations in non target genes • Depends on the tool used 	
(C) Manipulation of primary transcript in order to restore the reading frame disrupted by frame-shifting mutations (exon skipping)	<ul style="list-style-type: none"> • Oligos: chemistry dependent. The main target organs are kidney and liver. Thus far oligos are well tolerated in humans up to high doses. Transient thrombocytopenia has been observed • Sequence dependent: modulation of non target transcripts. Renal? Hepatic? Thrombocytopenia? • Using viral delivery: see A 	
(D) Translational read through of direct nonsense mutations by PTC124 (Ataluren®)	<ul style="list-style-type: none"> • Dysuria, constipation; hypertension 	Losartan/aminoglycosides/warfarin
(E) Upregulation of a homologous gene, <i>UTRN</i> , coding for utrophin, a protein that can functionally compensate for dystrophin	<ul style="list-style-type: none"> • Drug dependent (unknown so far) • Theoretical issues if upregulation achieves expression in a tissue which does not normally express the gene 	
2. Cell based strategy	Adverse events	Interactions
(A) Injecting stem-cell-like muscle precursors containing a wild type <i>DMD</i> gene from a normal donor (heterologous grafting)	<ul style="list-style-type: none"> • Immunological reactions, transfer of viruses (HBV, HIV, Jacob Creutzfeld) 	Likely necessity to immunosuppress long term
(B) Injecting stem-cell-like muscle precursors from the patient himself (autologous grafting) after ex vivo permanent correction of the defect	<ul style="list-style-type: none"> • Immunological reactions • When cells have been modulated using a viral vector: see 1A 	

Table 1 (continued)

B. Pharmacotherapy aimed at pathological hallmarks of the disease (symptomatic treatment)		
1. Inflammation	Adverse events (more than single cases)	Interactions
(A) General inhibition of inflammatory process (<i>corticosteroids</i>)	Hypertension, hypokalemia, hyperglycemia, infections, adrenal depression, growth failure, short stature, osteoporosis, fractures, cushing syndrome, skin atrophy, striae, acne, steroid myopathy, aseptic necrosis, glaucoma, cataract, depression, gastrointestinal ulcers, behavioral problems	Immunosuppressants, anti-diabetics, deterioration of myasthenia and channel diseases, live vaccines, CYP3A4-inhibitors, anticoagulants
(B) Downregulation of cytokines (<i>cromolyn</i>)	Dermatitis, exanthema, gastroenteritis, myositis, bronchial irritation, hypersensitivity reactions	
(C) Downregulation NFκB (<i>NSAIDs</i>)	Gastrointestinal, hypersensitivity reactions, headaches, depression, tinnitus, photosensitivity, hematuria, renal failure in pre-existing renal disease, hepatic damage, alveolitis	Aspirin, ketonolac, amikacin, gentamycin, rifampicin, quinolons, coumarins, heparin, antidepressants (SSRIs), phenytoin, ritonavir, zidovudine, cisclosporin, MTX, diuretics, lithium, pentoxifylline, probenecid, tacrolimus
2. Fibrosis	Adverse events (more than single cases)	Interactions
Inhibition of connective tissue deposition (<i>pirfenidone, halofuginone</i>)	<ul style="list-style-type: none"> • Pirfenidone : GI symptoms, photosensitive skin rash, fatigue, itching, dry skin, hyperpigmentation, headache, weakness • Halofuginone: At 1.5–2.5 mg, halofuginone was moderately tolerated, with incidence of gastrointestinal adverse events (nausea and vomiting) associated with dose increments. • Losartan: Hypotension, hyperkalemia, angioedema, hepatopathy, thrombocytopenia, anemia, dysgeusia, hallucination, renal dysfunction • Imatinib: leukopenia, anemia, thrombocytopenia, headache, nausea, anorexia, diarrhea, dermatitis, myalgia, arthralgia, fluid retention, dysgeusia, paresthesia, sleep disturbance, GER, hepatopathy, renal dysfunction, infections • 60 mg/kg: mild gastrointestinal complaints, including dyspepsia, loose stool, nausea, and vomiting 	<ul style="list-style-type: none"> • Losartan: renal and hepatic dysfunction, contraind. in renovascular diseases. Interacts with PTC124 metabolism • Imatinib: CYP3A4 inhibitors, anticoagulants
Downregulation of TGFβ (<i>losartan, iplex, imatinib</i>)		
Reduction of oxidative stress (<i>idebenone</i>)		
3. Loss of muscle tissue	Adverse events (more than single cases)	Interactions
Increase muscle growth (<i>valproic acid, antibodies to inhibit the muscle growth inhibiting myostatin protein- MYO-029</i>)	<ul style="list-style-type: none"> • VPA: drowsiness, hepatopathy, pancreatitis, thrombocytopenia, coagulation defects • MYO-029: hypersensitivity reactions, rash, urticaria • Hypoglycaemia, water retention (soft tissue swelling), enlargement of lymphoid tissue, tachycardia, carcinogenic? 	<ul style="list-style-type: none"> • VPA: ASS, potentially hepatotoxic drugs
<i>IGF-1</i>		
4. Normalize calcium homeostasis	Adverse events (more than single cases)	Interactions
Inhibition angiotensin converting enzyme (<i>ACE inhibitors</i>)	<ul style="list-style-type: none"> • Hypotension, renal impairment, dry cough, angioedema, rash, hepatopathy, hyperkalemia, thrombocytopenia, leucopenia, anemia, myalgia, arthralgia, secondary LE • Headaches, rashes, gastrointestinal dysfunction, hypersensitivity reactions • Bradycardia, SA- and AV-block, hypotension, edema, rashes, photosensitivity, hepatopathy 	<ul style="list-style-type: none"> • NSAIDs (renal damage), diuretics (hypotension), contraind. in renovascular dis. and heart valve stenoses, cardiac glycosides, ciclosporin, lithium, potassium • Analgesics, ketorolac, theophyllin, antihypertensives, antidiabetics • Alpha-Blockers, anaesthetics, anti-arrhythmics, erythromycin, clarithromycin, rifampicin, anti-epileptics, antifungals, antivirals, ciclosporin, tacrolimus, simvastatin, theophyllin
Modifying calcium channel activity (<i>pentoxifylline</i>)		
Calcium channel blockers (<i>diltiazem</i>)		
5. Necrosis	Adverse events (more than single cases)	Interactions
Downregulation of TNFα (<i>infliximab, etanercept</i>)	<ul style="list-style-type: none"> • Infection, tuberculosis, sepsis, nausea, diarrhea, heart failure, pancreatitis, hepatopathy, hypersensitivity reactions, secondary LE, aplastic anemia • Headache, nausea, fatigue, hyperbilirubinemia 	<ul style="list-style-type: none"> • Hepatic, renal, heart diseases; anakinra, live vaccines
Prevention of mitochondrial disruption (<i>Debio-025</i>)		

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Table 1 (continued)

6. Else	Adverse events (more than single cases)	Interactions
Sildenafil	<ul style="list-style-type: none"> • Dyspepsia, headache, penile erection, visual disturbances, raised intra-ocular pressure, hypersensitivity reactions • Cardiac ischemia/ 	<ul style="list-style-type: none"> • Cardiovascular disease, nitrates, epoprostrenol, iloprost, α-blockers, antivirals, nicorandil

inherited neuromuscular diseases, however, will require long-term treatment. Thus, there is not only a risk for acute side effects, but also a potential risk for side effects that arise from long term, cumulative use of these drugs. Some drugs have already been used for a long time to treat other diseases and for these side effects might be predictable, although disease-specific side effects could occur in any particular neuromuscular disorder. This could be due to different tissue distribution (enhanced uptake by muscle), a response to the genetic defect or simply because drugs are used in a different age group. Thus, when these drugs are used in patients with inherited neuromuscular diseases, a good monitoring system for known as well as new side effects has to be in place.

Although emphasis is put on efficacy outcome measures, for novel treatments the monitoring of side effects, especially in the long term, is as important as monitoring of other outcome measures. For some new treatments, it may be possible to anticipate side effects, based on those observed for treatments of a similar class of drugs. Nevertheless, for many drugs the most prominent side effects were not anticipated and the drugs used are very diverse (Table 1), making a single protocol to monitor all drugs impractical.

Already many patients are treated with a combination of drugs (and this will probably increase in the future). This makes it more difficult to properly monitor side effects, since it is difficult to assess whether a certain side effect is caused by a single drug or a combination of drugs. Thus, each patient may require their own monitoring plan based on the drugs used. The data collected from this are extremely valuable and datasets should be collected in a standardized way (see below). This could be facilitated by patient registries that are currently being set up for many NMDs within the framework of TREAT-NMD (<http://www.treat-nmd.eu/patients/patient-registries/global-registries/>). There could also be information available on long-term treatment for some drugs in other diseases (e.g. corticosteroid use in rheumatoid arthritis). It would be good to share information and compare notes between different medical specialties.

4. Post-marketing surveillance of novel treatments for neuromuscular disorders

As noted above, trials for drug registration are usually short, relative to the life-long treatment often required in inherited neuromuscular diseases. Thus, monitoring of outcome measures and side effects should continue after the drug is registered, preferably for the duration of the treatment. However, these post-marketing studies are challenging, especially for rare diseases.

Myozyme treatment in adult Pompe disease illustrates one approach to post-marketing study conduct. After the observatory LOPOS and the placebo-controlled LOTS trials in adult patients with Pompe disease (both coordinated by Genzyme), myozyme was registered, since there was sufficient proof of the functional effects of the treatment: significant improvement in 6 min walk test and forced vital capacity in treated patients [3]. After drug registration, the worldwide cohort of treated patients increased further and a strategy for post-marketing studies was set up [4,5]. In France, an existing registry was joined to a new “treatment” registry from Genzyme. The registry included the disease history and diagnostic data (muscle biopsy, enzyme activity and the molecular analysis) and the clinical features (muscle, respiratory, cardiac, neurological and gastrointestinal symptoms). In addition, standardized evaluations were performed to assess muscle impairment: 6 min walk test, manual muscle testing (MMT), quantitative muscle testing (QMT), muscle function testing (MFM) and respiratory function analysis. As before, non treated patients were assessed clinically once a year, while treated patients were assessed twice yearly. This disease registry, rather than being only a treatment registry, compared parameters in treated and untreated patients, and in single patients before and after treatment. This approach illustrates the value of patient registries that document the natural history of a disease even when no treatment is available.

Such post-marketing studies, which can be set up via the mechanisms already in place via the TREAT-NMD registries, are crucial for the evaluation of both short and long term tolerance for the drug and the validation of therapeutic benefit. In the adult Pompe disease cohort that was treated, the therapeutic benefit was clearly more modest than that observed in children [6,12,13]. Furthermore, there were groups of patients that responded better to treatment than others. This can have many causes (e.g. age of initiating treatment, residual enzyme levels, the formation of antibodies against the enzyme, the genotype etc.) and it is important to elucidate this further to optimize treatment for patient “subgroups”. This will become increasingly necessary considering that the cost of some of the novel therapies is considerable.

5. Combination of approaches

Having had few treatments in clinical trials for NMDs, now for some diseases (e.g. DMD) we are facing a new dilemma as clinical trial opportunities proliferate and the patient group eligible to participate in trials is limited. This

poses a risk of people dropping out of one trial to participate in a second trial testing another drug. Having people participate in multiple trials at the same time involves many practical and ethical questions, e.g. it will be difficult to assign the success to an individual drug, when a combination of drugs is tested. It will be equally difficult to assign side effects, especially if there are unanticipated effects that only arise when drugs are combined.

An additional issue is that the number of experienced clinical trial centers is limited. To allow more patients to participate in clinical trials, centers should be trained now, so they can be involved in future studies. Working with other established trial networks such as CINRG and the MSG, TREAT-NMD is seeking to facilitate this via its international care and trial site registry and associated training opportunities. Furthermore, the availability of sufficient patient numbers is a problem especially for the personalized medicine type approaches like exon skipping and PTC124 (ataluren[®]) [14]. For exon 51 skipping, two Phase I/II systemic trial using two different types of chemistry (PRO051 and AVI-4658) have recently been completed (<http://prosensa.eu/press-room/press-releases/2009-09-14-PRO051-shows-favourable-results.php>; and http://www.avibio.com/news_detail.php?newsId=0085, respectively). For both chemistries plans for pivotal placebo-controlled Phase III trials are being made. While patient registries facilitate recruitment into such studies, new challenges are anticipated, as new types of chemistries are being developed and these will need to be tested in the future as well. Even for exon 51 skipping – the personalized medicine approach applicable to the largest group of DMD patients (13%) [15] – there are not sufficient patient numbers to perform Phase III trials for the anticipated new generation of chemistries. Thus, a different pathway for clinical studies and regulatory approval is required to develop these new types of drugs. In addition, communication and transparency with patients is key. Not all patients are eligible to participate, e.g. 87% of DMD patients do not benefit from exon 51 skipping trials [15].

For the new approaches and combination of approaches having biomarkers to assess to monitor treatment and side effects would be very helpful. It is essential to assess these in early pivotal studies, to allow a correlation between biomarker levels and functionality. Equally important is the compiling of longitudinal datasets containing standardized parameters from patients, as well as compiling similar datasets of adverse events involved in trials globally. These issues were addressed in a recent meeting with the regulatory authorities [16] where a dialogue was established to consider a way forward to accommodate these specific issues – which are relevant much more broadly as personalized genetic based medicines are anticipated to become a bigger issue in medicine broadly.

Finally, for many NMDs, updated natural history data is not available, also due to the change in the natural history secondary to the improved standards of care. Collecting relevant events for patients worldwide within the

different genetic subtypes should facilitate the development of therapeutic approaches. While the TREAT-NMD global registry structure offers a way to facilitate this, funding for the maintenance of such databases is costly. The collection of longitudinal parameters could be initiated by funds from industry, charity and research funding agencies, as for drug registration these registries are essential. In the future, this should be build into the health system (as the information in the registries is also useful for reimbursements). Given the importance of registries, a good monitoring system should be in place as well. With appropriate information and consent, it is likely that patients will be willing to share their data with other parties to facilitate therapeutic development, but they should be involved as key stakeholders on how their data will be used.

6. Discussion

Since life-long treatment is required for neuromuscular disorder patients, life-long monitoring for efficacy and side effects, and registering these effects, is essential. The identification of side effects is as important as the assessment of beneficial effects and including a standardized way to measure side effects in a quantitative way should be taken into account during study design and long term follow up (rather than just focusing functional improvement or slowing down of disease progression).

Furthermore, the results from all clinical trials should be published. Trials with negative effects are often not reported, thus increasing the chance of unwanted repetition of testing drugs that are not beneficial. If trial data are owned by industry, it is their prerogative whether or not to publish. One solution could be to make publishing a trial and trial results imperative. Even with negative results, the data can be used for other analyses and are thus still useful to others. Indeed we recommend long term follow up of patients involved in all clinical trials initiated in our field via a mechanism such as the TREAT-NMD registries. It is possible that the really life altering effects of treatments (efficacy or side effect) will not become apparent during the usual follow up period of 6–12 months, but become significant after many years.

Long term follow up is a major commitment for all concerned, starting with the patient and family. While many clinicians may be willing to perform life-long monitoring, this involves time and money, which are mostly lacking for clinicians, who generally perform clinical trials in addition to their normal clinic duty. To give an example, the Pompe registry that will monitor patients over 15–20 years, costs millions of Euros per year to maintain. Ideally, the pharmaceutical companies would sponsor these initiatives indefinitely – though here is a cost issue as well, as the companies developing treatments for neuromuscular disorders are generally small and they may not be able to afford this. It would probably be more cost efficient to appoint an academia based coordinator to oversee the data collection (on efficacy and side effects of treatment) and to maintain

the database for a specific drug. Alternatively, each clinical trial center could appoint a study nurse to coordinate data gathering for all studies ongoing at that centers. Such people could be (partly) funded by the companies developing the drugs and/or patient organizations and by sharing of resources costs could go down and databases could be managed more efficiently. Given the imperative of having these longitudinal studies for drug development, the best solution would be for health care to cover these costs.

The key to success when developing therapeutic approaches is good communication, commitment and partnership between all stakeholders: researchers, clinicians, industry and patient organizations.

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