

CLINICAL TRIALS IN DMD- FROM PHASE 1 TRIALS TO CLINICAL BENEFIT ASSOCIATION MONÉGASQUE CONTRE LES MYOPATHIES & DUCHENNE

Parent Project France, Round Table
June 23rd 2007, Monaco
by Katie Bushby



This meeting was the 6th Round Table organised by the Association Monégasque contre les Myopathies & Duchenne Parent Project France, and was attended by 21 scientists and industry representatives and 10 patient organisation representatives. The remit of the meeting was to discuss the progress from early phase 1 trials in DMD to the development of therapies in clinical use. Presentations covered the current state of the art with respect to ongoing or completed phase 1 trials, including myostatin inhibition, stop codon read through, the sarcoglycanopathy AAV trial and trials of antisense oligonucleotide induced exon skipping. Ongoing preclinical studies related to AON, AAV U7, high throughput drug screening for drugs which might enhance exon skipping and the use of muscle precursor cells were also presented. General discussion focussed on the issues surrounding the large scale production of clinical grade AAV and AON, and the potential long term toxicity or immunogenicity of these agents. There was also a short discussion about the requirements for the execution of clinical trials, and the TREAT-NMD network was presented.

Participants at the meeting recognised the exciting stage that preclinical and early clinical studies in DMD have reached. Some basic methodological questions in common with many of the trials were relevant to the TREAT-NMD objective of accelerating trials in DMD. Some of these were very basic and could begin to be answered as the experience from the early trials accumulates. In terms of measuring dystrophin expression, sharing of Western blotting protocols for standardisation and cross comparison could be useful through the designation of SOPs and/or reference laboratories, while the lack of correlation of dystrophin levels to physiology and function also remains poorly understood. In planning a muscle biopsy, the variability of response of different muscles to systemic treatment seen in animal models is very important for biopsy outcomes including choice of muscle and timing of biopsy, and this could be helped by further definition of non-invasive methods for determining the response of different muscles to treatment. Equally, it needs to be determined how large animal studies might contribute to the understanding of bioavailability and dosing data for the different compounds. There remains a requirement to define and agree clinically significant and disease specific outcome measures.

Several issues were identified as particularly important for dialogue with the regulatory authorities. As this is a relatively new area for clinical trials, there was a feeling that there was a need for the regulatory authorities to understand the implications of studies in these diseases. Given the untreatable and progressive nature of the disease, can there be any systematic approach to reduce the regulatory timelines? In any specific situation, what preclinical evidence is going to be needed and when will intermediate steps between for example mouse and human be required? The species in which it will be mandatory to perform toxicology studies remain to be defined. A major issue as

so many new therapies with mutation specificity are on the horizon is the limited patient numbers-how does this impact on regulatory issues as there will be only small patient cohorts for each targeted therapy, with the potential need for innovative trial design. Another issue we need to understand is whether if one therapy is shown to be effective will it de facto be regarded as the gold standard and other modes have to be compared. Approaches to therapy are required which will be applicable to all boys with DMD, at different stages of the disease.

This meeting was the first of a series of meetings on related topics which have taken place over the past ten days in which TREAT-NMD has been represented and these will be reported in successive newsletters. The need for dialogue amongst all the stakeholders from patient organisations to industry is particularly important, and the Monaco meeting as always allowed the development of fruitful discussion. Many thanks go to Luc Pettavino and Christine Dattola for their hospitality.

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