

FOR- DMD- double blind randomized trial to find optimum steroid regime

MSG/ TREAT-NMD collaboration

The story of the trial started in 2003.....

- Inconsistency in corticosteroid dosage regimes for DMD identified as top priority by ENMC clinical trials unit
- ENMC workshop convened April 2004 (KB, RG, AU)
- Aim- to define the need for clinical trials of steroids in DMD and devise a protocol
- Attended by representatives of 12 countries (clinical, parent reps)
- International steering group with patient organisation support and several working groups for trial design
- NIH planning grant 2005, full grant submission 2007, resubmissions June 2008, 2009, final funding decision September 2009
- Inconsistency in use of steroids remains a major clinical problem and may be a threat to the ongoing trials of innovative therapies

Primary study objective

- The proposed randomized controlled trial will compare 3 corticosteroid (CS) regimens to address the pragmatic hypothesis that daily CS (prednisone [P] or deflazacort [DFZ]) will be of greater benefit in terms of function and patient/parent satisfaction than intermittent CS [P].

Secondary study objectives (1)

- A second hypothesis is that daily DFZ will be associated with a better side effect profile than daily P. The study protocol includes standardized regimens for prevention/ treatment of predictable side effects of CS medication, as well as baseline standards of care for the general management of DMD.

Secondary study objectives (2)

- The trial directly addresses the current chaos in prescribed treatment schedules; its results will have direct impact on the current and future management of boys with DMD throughout the world by providing the evidence base for rational clinical practice.

Design and Outcomes (1)

- This is a multi-center, double-blind, placebo-controlled, parallel group, 36-60 month study, comparing three regimens in wide use in DMD.

Design and Outcomes (2)

- The primary outcome variable will be a three-dimensional (multivariate) outcome consisting of the following three components (each averaged over all post-baseline follow-up visits through Month 36): (1) time to stand from lying (log-transformed), (2) forced vital capacity, and (3) subject/parent global satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication.

Design and Outcomes (3)

- Secondary outcome variables will include regimen tolerance, other timed function tests (including 6MWT); cardiac function, quality of life, and adverse event profile.

Interventions and Duration (1)

- The trial will randomize 300 boys aged 4-7 years to 0.75 mg/kg/d prednisone; 0.9 mg/kg/d deflazacort; or 0.75 mg/kg/d prednisone for 10 days alternating with 10 days off. All boys will complete a minimum of 3 years (36 months). All boys entering the trial will remain on study drug until the last boy completes the 36 months of study. This may be up to 60 months.

Sample Size and Population

- A sample size of 100 subjects per group (300 total) will provide adequate power to detect differences that are thought to be of minimal clinical significance between any two of the three treatment groups, assuming a 10% rate of subject withdrawal.

Trial organisation

- MSG data management and statistics, NIH communication
- Newcastle CTU master files etc
- TREAT-NMD trials co-ordination centre training, dissemination of information, site initiation, monitoring

Interaction with new treatments?

- Further phase I/II/III trials will be initiated in the course of the trial
- Consent needs to be sensitively worded to take this into account
 - Challenge to the regulatory authorities??
- Also clear commitment to review new developments in the course of the trial
- Could be major issue in recruitment
- Site selection will need to take this into account

Opportunities

- Inclusiveness of participation
 - 12 countries represented
 - Consolidation of MSG/ TREAT-NMD collaboration
- Innovative set of outcomes to reflect functional and respiratory outcomes as well as satisfaction with medication
- Maximum possible control of side effects
 - Standardised input on diet, behaviour, bone etc
 - Will address broader issues of standards of care
 - Major training opportunity for sites to develop experience on trials, standardisation of care standards
- Adjunctive studies addressing pathophysiology