Dose-Toxicity Study of Oral Prednisone in Ocular Myasthenia

Michael Benatar, Mike McDermott,
Gil Wolfe and Don Sanders

Background

- Goals of therapy

  - Restore clear state of vision

  - Reduce the risk of progression to GMG

- Absence of data

  - Evidence Report: Medical Treatment of Ocular Myasthenia (Neurology 2007 68:2144-2149)

  - Treatment of Ocular Myasthenia (Neurology, 2008, in press)

- Clinical equipoise

  - Need to balance potential efficacy against potential for steroid side effects

The Controversy

- Do the benefits of steroids outweigh the risk of steroid therapy?

  - Do ocular symptoms impair QoL or cause functional limitations?

  - How effective is pyridostigmine?

  - How effective are steroids?

  - How frequent/severe are steroid side effects?

Study Design

- Enroll patients with newly diagnosed OM

- Treat with pyridostigmine x 1 month

- Randomize those whose symptoms fail to remit to one of two steroid dosing strategies

- Aggressive prophylaxis and treatment of steroid side effects

- Steroid treatment x 6 months

- Titrate steroid dosage against symptoms

- Quantify impact of symptoms & Rx on QoL

Specific Aims

- To select a tolerable steroid dosing strategy for an efficacy study

- To demonstrate the adverse impact of ocular symptoms on QoL

- To validate the ocular-QMG as an outcome measure

- To estimate the proportion of subjects whose ocular symptoms remit

Inclusion Criteria

- Weakness confined to extra-ocular muscles, levator or eye closure

- At least one abnormal diagnostic test

- Inadequate prior pyridostigmine treatment (dose not titrated to efficacy or intolorability)

- Age > 18; male or female

- Identifiable internist (to manage steroid AEs)

Exclusion Criteria

- Steroid treatment (> 10mg/day x 30 days)

- Current immune suppression

- Prior thymectomy

- Contra-indication to steroids (e.g. poorly controlled diabetes, HTN, glaucoma)

Outcome Measures

- Primary

  - Ability to remain on prednisone for study duration without the occurrence of an adverse event that does not resolve with appropriate therapy or dosage reduction

- Secondary

  - Quality of Life - INQoL

  - Ocular-QMG- reliability & validity

  - Subjective global impression of change

  - Time to MM & to ocular-QMG score of 0

Relevance to Efficacy Study

- Selection of tolerable prednisone dosing strategy

- Demonstration of impact of ocular symptoms and treatment on QoL

- Validation of ocular-QMG as outcome measure

- Enrollment/recruitment feasibility

Discussion

- Is the problem at important one?

- Is prednisone the best therapeutic choice?

- Is it worth studying two prednisone dosages?

- Phase II → III versus phase II/III

- Collaborative opportunities

    - Collect QoL data

    - Subject eligibility & willingness