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Introduction

Preventing familial ALS: A clinical trial may be feasible but is an efficacy trial warranted?

In this issue of JNS, Benatar et al. have proposed targeting a trial to a subgroup of the ALS-susceptible population. This approach will become more common in this evolving era of pharmaco-genomics. They should be congratulated in taking these ideas almost always limited to the predictors of response (often post-hoc) to the design stage.

In the United States, the prevalence of ALS is 4–6 cases per 100,000 with an incidence of 0.4–1.8 per 100,000. The majority of cases are sporadic; however familial ALS (fALS) affects 2–15% of all cases of ALS, often with an autosomal dominant inheritance pattern. Mutations of the SOD1 gene account for approximately 20% of the familial cases. Thus, when focusing on fALS, we are discussing at the upper limit about 5.4 cases per 10 million adults.

In this issue of JNS, a survey study by Benatar et al. identified 116 families at risk for fALS including 516 patients with ALS, 169 from SOD1-positive families, as well as 335 at risk from SOD1-positive families. The authors state that approximately 80–90% of the at risk population were willing to participate in a clinical trial. The proposed clinical trial would have a follow-up period of at least 5, possibly 10 years. Therefore, it is imperative to consider long-term factors other than initial enrollment, including retention. Furthermore, addressing the impact of side effects in a still healthy population is important as in other prevention studies; however it does potentially limit the choice of interventions and requires the ethical issues associated with gene testing and treating still healthy subjects. In the proposed trial the primary outcome is incidence of disease so from that perspective disability is less of an issue. This enhances the fact that there was no provision for dropouts made in this manuscript.

ALS clinical trials generally have fewer problems with initial recruitment, but this is in part due to the poor prognosis and increasing disability presented by the disease. In a prevention trial using unaffected relatives, compliance and attendance when the benefits to the therapy are not perceived may not be as optimistic. Furthermore, the complexity of non-independent cases or family members may need to be taken into account. Would family members be guaranteed the same treatment? If yes, then there may be highly correlated dropouts because once a case develops, the entire family may feel the treatment has failed and see no reason to continue therapy.

It would be essential to look further at the practicality of such a study. Even if a therapeutic agent could prolong time of onset of fALS by 50%, it would necessitate a sample size of 254 subjects, while a drug with 40% effectiveness would need an increased sample size of 437 per group, and for a more realistic 30% effectiveness: 849 subjects would be required. To date the only medication shown to have an effect on survival in ALS is riluzole which increases life expectancy by an average of 3 months, roughly a 5–10% improvement in survival. The sample size needed for an agent with this effect size would approach 3000 per group.

Therefore at this point in time, it is unclear that enough fALS at risk individuals could be recruited in order to show efficacy using a drug with a modest effect. Recent review of neuroprotective agents for ALS (Neurology, Vol. 67, No. 1: July 2006) have identified 20 drugs which may be suitable for further development in ALS and pharmaceutical companies are pursuing a dozen others. Combination studies theoretically show promise for further benefit in murine models, but a first human ALS combination trial using agents successful in rodents is just getting underway (personal communication, Gordon et al.). Still the effect size in studies planned for ALS or even in successful MS and epilepsy trials rarely exceeds 30%.

The benefits of doing a study of at risk familial ALS subjects are many. The logic presented by Benatar et al. should not be lost. Targeting specific therapies that focus on the origin or promulgation of the mutation or the consequences of the mutation, for example decreasing SOD1 production with drugs or gene therapy may yield greater successes and larger effect sizes. The experimental animal models often used to find agents are more closely allied with fALS. Further, this type of study could substantially improve the life span of at risk SOD1 family members, improve or impact their quality of life by allowing them to do something proactive and potentially beneficial and aid in our understanding of fALS. However the ability to generalize on the more prevalent sporadic form of ALS is still unclear and yet mounting a trial fALS may signal false hope for sporadic

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ALS. Without the side effect information and potential negative consequences of a preventive procedure in averting a rare disease may not be the best strategy. If a future clinical trial includes the possibility of revealing the results of genetic testing, careful attention to consent related issues becomes vital. As the authors point out, it will be essential to provide appropriate counseling to explain the risks and benefits of obtaining genetic information and to discuss variable phenotypic penetrance.

One possible solution would be to perform a staged Phase II–III study with the vanguard Phase II population used to evaluate multiple doses to identify the maximum tolerated treatment dose. Safety and tolerability would be the endpoints and would require fewer subjects. A Phase II study could provide a hint of activity; however it is highly unlikely that efficacy could be found using the US population alone. Both NIH and industry have been exploring more global populations particularly to complete efficacy studies with sufficient numbers of subjects. Unfortunately the SOD1 mutation is not commonly seen in other parts of the world. Still, it may be useful to undertake further surveys of international patients and establish international collaborations that could yield sample sizes necessary for an efficacy study in fALS.

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