

Placebo Design Clinical Trial in Neuromyelitis Optica IS ethical.

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Many considerations are in play when exploring the most appropriate design for a randomized, controlled study in NMO, a design that balances the need for scientific rigor with the safety of participating patients. The two most significant considerations related to placebo-controlled design are those related to the ethics of clinical trials and those related to what constitutes “standard of care.” These two issues, ethics and standard of care, are closely related to each other in the context of assessing the appropriateness of clinical trial design.

NMO is a serious disease, and attacks may lead to devastating neurological consequences. There have been no randomized, controlled trials in this disease to direct decision-making; physicians committed to treating patients have adopted immunosuppressive medications approved for use in other autoimmune diseases. The fundamental question is whether the use of a number of available immunosuppressive medications, unapproved for NMO/NMOSD, constitutes a “standard of care” and can be used as an active control and/or background therapy in randomized, controlled trials for new treatments for NMO/NMOSD.

The WMA Declaration of Helsinki #33, October 2013 states: “Use of placebo is appropriate where no proven intervention exists and where for compelling and scientifically sound methodological reasons, the use of any intervention less effective than the best proven one is necessary to determine the efficacy and safety of an intervention.

In this systematic review, out of 2,438 citations noting NMO/NMOSD, 77 primary studies met the inclusion criteria. Of those, 49 were studies of maintenance therapy to prevent NMO/NMOSD relapses. The systematic review demonstrated that ALL studies that assessed current unproven treatments to prevent NMO/NMOSD attacks are Class IV studies (the lowest) which includes all published Rituximab, AZA, and Mycophenolate Mofetil studies. This means that all published studies were uncontrolled, small, retrospective observational studies.

Also, benefit/risk assessment for NMO/NMOSD maintenance therapies cannot be determined based on the published studies because of the minimal reporting of safety evaluations. Therefore, based on this systematic review, all current unproven treatments used to prevent NMO/NMOSD relapses meet Level “U” of the AAN treatment guidelines and do not meet the criteria for establishing clinical guidelines, and probably cannot be referred to as “standard of care”.

It is clear that the lack of evidence for treatments in NMO/NMOSD is a significant factor in establishing the ethical basis for a placebo-controlled study. A low level of evidence and lack of “standard of care” are grounds for reasonable professional disagreement among physicians as to the appropriate clinical approach for this disease. The status of disagreement, the “Clinical Equipoise,” provides for an ethical argument that aims at reconciling the overall needs and interests of the “NMO society” with the duties and rights of physicians and patients. When equipoise exists, it is considered ethical to offer physicians

and patients the option to participate in a placebo-controlled study, and at the same time, the option to not participate in such a study.

To enhance open discussion and the exchange of ideas on the ethical grounds for a placebo controlled study in NMO, a sponsored public open symposium was held at the European and American Committee on Treatment and Research in Multiple Sclerosis (ECTRIMS/ACTRIMS) meeting in Boston on 11 September 2014. This open forum provided a stage for the spectrum of opinions related to the ethical grounds for a placebo-controlled design, which were presented by a range of established experts in NMO and ethics. This symposium highlighted the current state of disagreement among the main stakeholders of this important dilemma, and concluded with the recognition that the current state of clinical equipoise gives ethical legitimacy to a placebo-controlled design for those physicians and patients who decide to participate in such a study. The European Medicine Agency (EMA) conducted a NMO workshop in October 2014 in London which included the participation of NMO expert physicians, ethicists, pharmaceutical representatives, European regulators and patient advocacy group representatives. In this workshop, Dr. Simon Woods, co-director of the policy ethics and life sciences research institute at Newcastle University, summarized what would be required for giving a placebo-controlled design to be ethically justified: Clinical equipoise in place, least possible exposure to placebo, Cross-over/open-label extension, appropriate form of ethical review, consultation with patient groups. Dr. Woods concluded that indeed clinical equipoise is in place in the case of NMO, and those public forums like the EMA NMO workshop, and the ethical symposium in Boston are an appropriate way of ethical review.

The use of a placebo controlled trials in NMO and its inherited ethical controversies have led to several recent publications from NMO experts and ethicists analyzing the acceptability of such trial design in this disease (Cree B, 2015; Rhodes R, 2015; Greenberg B, 2015; Weinshenker B, 2015; Palace J, 2015; Levy M, 2015). The authors also analyzed the ethical concerns regarding the harm, benefit and justice of a placebo design in NMO patients as individuals and as the population living with the disease and its implications to treating physicians. Rhodes and Cree concluded that ultimately the choice to participate in a placebo trial comes down to the patient and physician after providing a full informed consent. Rhodes concluded that reluctance to undertake these types of studies benefits neither the potential subjects of the study nor the patients outside the study living with NMO and provides a barrier to the advancement in NMO research.

Placebo designed study in NMO should be done with the aim of striking a balance between patient safety and clinical/scientific integrity. Specific measures should be implemented into the study design to mitigate the concerns related to a placebo-controlled study such as short exposure to placebo, unequal randomization, immediate access to rescue therapy, and occurrence of a single relapse as a primary endpoint.

In summary, a placebo design study in NMO is ethical and meets all GCP guidelines. This type of a study should be offered to patients and physicians and although not all physicians and patients will choose to participate in such a study, they should have the opportunity to make this decision,