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The ethics of placebo controlled clinical trials in NMO – A balance of risks

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“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists”.

– Section C, Paragraph 29 of the Declaration of Helsinki (17.C) Taken literally, the Declaration of Helsinki would have prohibited almost any therapeutic clinical trial with a placebo control group if a proven therapy currently exists (Levine, 1999). However, most physicians agree that the ethics of conducting a placebo-controlled trial also depends on the disease being studied. Few would object to a placebo arm if the consequences of not treating were reversible or mild. In a disease where the consequences are more severe and can lead to permanent damage, the ethics are clearer. The United States Food and Drug Administration’s FDA (2001) Guidelines to Industry states, “In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally in-appropriate to use a placebo control. There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients have refused to receive it (FDA, 2001).”

In applying these ethical principles to neuromyelitis optica (NMO), it is important to understand the historical context. NMO is an autoimmune disease that targets the optic nerves and spinal cord leading to blindness and paralysis (Oh and Levy, 2012). Until a unique biomarker for NMO was discovered, NMO was previously thought to be a severe variant of multiple sclerosis (MS) that did not respond to traditional MS therapies. Neurological disability in NMO is caused by permanent damage to the optic nerves and/or spinal cord due to repeated inflammatory attacks. Untreated, 60% of NMO patients are blind in at least one eye and 52% are paralyzed in at least one limb within 8 years of diagnosis, and the mortality for NMO in 1999 was 32% (Wingerchuk et al., 1999). Adjusting for milder cases now recognized to be in the spectrum of NMO would likely reduce these

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numbers, but they remain well above the morbidity and mortality for MS. Out of concern for any single relapse likely causing blindness or paralysis, expert physicians and researchers have historically been weary of a placebo-controlled trial in NMO.

The announcement of a placebo-controlled trial in NMO landed like a bombshell in July 2013 when two companies interested in launching registrational phase 3 trials were told by US FDA regulators that the agency strongly prefers a pivotal monotherapy, placebo-controlled arm rather than the add-on or head-to-head designs initially proposed. The FDA's judgment was in direct contrast to rulings by the European Medicines Agency (EMA), Japan's Pharmaceutical and Medical Devices Agency (PMDA) and the viewpoints of academic, industry and patient-advocacy groups at the time. The FDA's primary concern was that widely used therapy was not sufficiently supported by trial evidence and should be considered experimental rather than "standard of care." Faced with the potential loss of revenues from the US market, the two companies decided to try accommodating the FDA's request and recruited supporters within the NMO expert community to help them revise the trial design to include an ethically palatable placebo arm. The FDA's insistence on a placebo arm in any pivotal study in NMO caused a schism in the NMO community along ideological lines (placebo advocates vs. placebo opponents), and so began the debate on the ethics of placebo-controlled trials in NMO. Regardless of the motivation for re-designing the first two trials with placebo arms, a debate of its ethics is timely as patients and clinicians begin to consider whether to participate.

Although there are no historical placebo-controlled or blinded trials in NMO to presently guide treatment, there is strong sentiment that all patients should be offered immunosuppressive therapy. Advocates of placebo controlled trials in NMO do not dispute that relapses in NMO can often be severe, permanent and devastating; many of them are clinicians who have published observational studies on potential therapies that may treat NMO. Opponents of placebo-controlled trials in NMO emphasize the remarkable consistency and degree of response to off-label treatment. Indeed numerous studies conducted around the world demonstrated dramatic benefits in using immunosuppressive drugs to prevent relapses and achieving clinical remission without significant tolerability issues. The most notable example of a purportedly effective immunosuppressive drug in NMO is rituximab, a monoclonal antibody that depletes circulating B cells. Since 2007, more than a dozen longitudinal series between 5 and 100 adults and children have unanimously declared significant reductions in disease activity. Other immunosuppressive treatments have been studied as well, including mycophenolate, azathioprine, methotrexate, mitoxantrone and prednisone – all show some measure of efficacy in retrospective series. In 2012, 15 worldwide NMO experts in the field reviewed the available literature and authored a manuscript detailing specific immunosuppressive regimens for the treatment of NMO, including rituximab (Kimbrough et al., 2012). The EMA, PMDA and other national agencies have also weighed the available evidence and determined that proven therapy does exist for NMO.

The US FDA reviewed the same evidence and concluded that it does not meet the criteria for standard of care, and indicated that a placebo-controlled trial is therefore preferred. The FDA insists that since no unbiased, placebo-controlled trials have ever been conducted in

NMO, there cannot be a standard of care. In order to be sure that the new experimental drug is effective, the FDA needs to compare efficacy data of a new experimental drug to placebo or a control that has been previously evaluated against placebo. Falling in line behind the FDA, placebo advocates agreed that sufficient clinical equipoise (i.e., uncertainty) exists within the field that makes placebo-controlled trials necessary, despite the extensive class IV evidence of the benefit of a handful of immunosuppressive medications.

Opponents of placebo-controlled trials do not deny that placebo-controlled trials are more scientifically sound. Many placebo opponents are scientists who run laboratories in which placebo designs are required to prove concepts in animal models; they acknowledge the rigor and certainty that placebo controls provide. However, placebo opponents argue that patients are not animal models and require a higher threshold of uncertainty to justify a placebo arm. They maintain that even if the FDA is not absolutely certain that the current standard of care is effective in NMO, there is an abundance of evidence to meet the mandate of the Declaration of Helsinki to offer proven therapies to all patients.

The debate on the issue of standard of care has reached an impasse. Advocates of placebo trials continue to claim the higher scientific ground by criticizing previous studies as biased. Opponents of placebo trials stand firm in their conviction that perfect is the enemy of good; i.e., they resist calls to dismiss the hard-earned progress made in treating NMO and to pretend that no treatments are effective. And then there are those in the middle of the spectrum who preferably trust placebo-controlled trial data but are concerned about the risk of a placebo arm in a disease like NMO. As this debate evolved over the past two years, a middle group of moderates has grown from both sides as new placebo-controlled trial designs have emerged with means of ameliorating the placebo risk to each individual subject. Placebo risk to patients can be reduced by both improving the odds of randomizing into the experimental arm and by limiting the time in the placebo arm.

Industry groups and placebo advocates like to claim that placebo controlled trials reduce the overall risk to the NMO trial community because placebo controlled trials would require fewer patients and fewer on-trial relapses. That argument is based on the assumption that head-to-head or add-on studies use immunosuppressive medications that are effective in suppressing NMO disease activity and falls apart if previous studies are dismissed as experiential and biased. Without considering previous evidence in NMO, placebo controlled trials and head-to-head studies would require the same number of subjects and on-trial relapses. Nevertheless, this argument should be ignored when sitting face to face with NMO patients. Clinicians must only consider only the best interest of their individual patients. "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society" (Declaration of Helsinki, 2000).

By combining the available data on standard of care for treatment of NMO with the novel trial designs that seek to reduce the risk for placebo patients, patients can compare the risks imposed by standards of care and experimental therapies. Assuming an experimental therapy is as effective as rituximab based on available case series and open-label prospective studies, Table 1 provides a comparison of risks. For example, an experimental drug as effective as

rituximab (relapse risk of 17%) randomized 3:1 – 75% chance of receiving drug – would be equal to $1-(0.75 \times (1-0.17))$, or 38% relapse risk. For the same drug randomized 2:1 – 66% chance of receiving drug – the relapse risk would be $1-(0.66 \times (1-0.17))$, or 45%. According to this menu of treatment options, rituximab is the clear winner and should be offered as a first line agent where the drug is available. If patients refuse, cannot tolerate or are otherwise unable to obtain rituximab, other standard agents including mycophenolate and azathioprine provide meaningful benefit, but with increased risk of relapse. Weighing alternatives to rituximab listed in the table, experimental options may be in the best interest of the patient, even if the trial is placebo-controlled, especially if the risk of relapse is reduced further by limiting the exposure time to the placebo arm. This table may be used to guide patients and clinicians when considering enrollment for patients in NMO trials.

In the end, we all want to conduct the best clinical research and learn as much as we can from our patients, while at the same time, protect our patients from harm as best as we can. Realistically, a moderate approach to placebo-controlled trials in which calculated risks from trials can be weighed against proven standard options ultimately achieves the best for the most.

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Table1

Calculated risks of relapse with standard and experimental placebo-controlled trial options. (Calculated from Mealy et al.,2014).

Drug	Risk of relapse (%)
Rituximab (standard)	17
Mycophenolate mofetil (standard)	25
Experimental drug, 3:1 randomization	38
Experimental drug, 2:1 randomization	45
Azathioprine (standard)	53
Experimental drug, 1:1 randomization	58