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A placebo controlled trial for an NMO relapse prevention treatment: Ethical considerations

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ABSTRACT

This paper addresses the ethical acceptability of a proposed placebo controlled trial of a new intervention as a possible relapse prevention treatment for Neuromyelitis Optica (NMO). In the analysis of this controversial ethical issue, the author points out significant factors that are often overlooked or ignored, such as the life-long implications for study participants and others living with the disease, and also addresses commonly noted issues, such as vulnerability, benefits, harms, and justice that always require attention in research review.

1. Introduction

When I was invited to offer comments on a placebo controlled trial of a potential relapse prevention treatment for Neuromyelitis Optica (NMO) at the ECTRIM Symposium in Boston on September 11, 2014, I had never heard of the disease. In fact, it took me two days to learn to say “Neuromyelitis Optica” without tripping over the syllables. Nevertheless, because I have been teaching research ethics for more than 20 years, and because I have published more than 20 papers and chapters on research ethics, I accepted the invitation. And because ethical judgments always turn on the facts, I set about learning. In the limited time available, I read what I could find, with only a partial comprehension, and I spoke to three neurologist colleagues to ascertain their positions on the issue.

Disclosure requires that I reveal that I am a bioethicist, a philosopher who has been teaching in a medical school for 27 years. I have no professional training in either science or medicine. I say this because even though I have made a sincere effort to understand this complex issue, I may not have fully understood the science or the medical issues. For those who believe that my reasoning is flawed, however, it is incumbent on them to provide reasons that explain where my arguments have gone astray.

2. Ethics

Ethical judgments are conclusions, not starting points. Judgments about the ethical acceptability of a research study follow from reflection on the relevant factors that require assessment. Unlike science, however, there is little consensus in the research ethics community on what those considerations are. Most everything in ethics and research ethics is controversial, and the ethical acceptability of placebo controlled trials is especially contentious. With that caveat, here is my list of the relevant factors that should be taken into account in this deliberation. In a determination of whether a research project is ethically acceptable, I believe the scientific factors, the expected benefits and harms to study participants and the affected population, as well as justice, and feasibility elements need to be considered. In what follows, I shall address these issues in turn.

3. Scientific factors

Several scientific factors should be addressed in any assessment of the ethical acceptability of conducting a placebo controlled study of a relapse preventing intervention for NMO. They include the impact of the disease and its natural history, the clarity of diagnosis, the evidence of safety and efficacy for available treatments, and the prevalence of disease.

3.1. Impact of NMO and its natural history

From my reading I have learned that NMO is an incurable disease. In more than 90% of patients, NMO is a relapsing disease with attacks of optic neuritis and/or transverse myelitis. It is disabling, with poor remission leading to rapid accrual of irreversible neurological disability. In studies from 1977 to 1997, 60% of patients exhibited severely impaired ambulation or blindness in at

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least one eye after 7–8 years. Only 68% of patients survived for five years after diagnosis (Jarius et al., 2014).

The natural history of NMO is relatively unpredictable. Disabling damage accrues during acute attacks, and relapses tend to occur in clusters after periods of remission. Periods of remission, however, can last for years even when patients receive no treatment (Kimbrough et al., 2014). In a few patients, the disease takes a relatively benign course, with only minor disability for up to ten years (Jarius et al., 2014).

Patients with NMO have a more severe disease than patients with relapsing-remitting multiple sclerosis (RRMS), including a higher risk of dying of a demyelinating disease. One study that compared both conditions at the same center found that the age of onset for both diseases was the early 30s with a mean survival of NMO patients of 7.4 years and 10.3 years for RRMS patients. Disease progression in patients with NMO was higher than in patients with RRMS (0.9 versus 0.6), and patients with NMO experienced significantly more disability on the expanded disability status scale (EDSS) than patients with RRMS (39% versus 17%) (Bichuetti et al., 2013).

3.2. Clarity of diagnosis

NMO is and has been commonly misdiagnosed. In 2004 an antibody biomarker for the disease was discovered (Lennon et al., 2004), and it became widely used by 2006 (McKeon et al., 2009). Nevertheless, uncertainty as to diagnosis persists. A multi-center cohort study of 187 patients found that 30% of patients were initially misdiagnosed as having MS. This is especially problematic because some MS treatments may worsen NMO (Mealy et al., 2012). Furthermore, many patients who are diagnosed with NMO do not have the biomarker. Depending on the study, the percentage of NMO patients without the biomarker can be very low or as high as 80% (Jarius et al., 2014; Thomas et al., 2012; Mealy et al., 2012; Kitley et al., 2012).

3.3. Evidence of efficacy and safety for available preventative treatments

Relapse prevention therapy for NMO has focused on a variety of immunosuppressive medications. None of them have been validated in a rigorous randomized trial (Kimbrough et al., 2012; Trebst et al., 2014). Systematic reviews of the literature have, however, produced treatment recommendations. One review revealed that the studies that claim to offer evidence of efficacy are all based on findings rated Evidence Level III or IV because all of these findings are based on either small numbers of subjects or retrospective reviews (Sato et al., 2012). In some studies, the number of participants was as few as seven. And the diagnostic uncertainty for NMO muddies the waters yet further, because it is not clear whether the subjects in the retrospective studies that included data from prior to 2006 actually had NMO.

Furthermore, in combining the results of several different retrospective studies, different follow up periods were used. It is also not clear that the studies employed the same criteria for diagnosis or the same criteria for defining a relapse. And it is not clear whether the disease state of the participants was comparable, whether the baseline and improvement measures were taken at the same points, and whether disability was measured in the same way. In sum, assay sensitivity, the ability of a study to distinguish between active and inactive (i.e., effective and ineffective) interventions, has, thus far, not been established.

In addition to questions about the efficacy, the six currently recommended drugs are also associated with significant side effects for short-term use. Yet, given the current thinking, NMO patients are likely to be treated with these drugs for the rest of their lives. This raises concerns about their safety for chronic use. As far as I can tell, the side effects of long-term use has not been studied, so the risks may increase with the duration of use. In short, in my review of the side effects associated with the six recommended drugs for NMO relapse prevention I learned that there are significant harms associated with all of these treatments and no data on their long-term use.

Preventive therapy drug	Side effects	Median follow up
Azathioprine	Lymphoma,nausea, elevated transaninases, leukopenia, diarrhea, bone marrow suppression, fatigue, hair loss, hepatotoxicity	9–42 months
Mycophenolate Mofetil	Headache, constipation, bruising, anxiety, hair loss, leukopenia, diarrhea, fatigue, hair loss, skin malignancies, lymphoproliferative disease	24–27 months
Rituximab	Recurrent herpes zoster, UTI, respiratory infection, fatigue, transient leukopenia, transient transaminase elevation, infections, transient hypotension, transient flu-like symptoms, allergic reaction	12–24 months
Methotrexate	Infections	6–62 months
Oral Corticosteroids	Hyperglycemia, hypertension, insomnia, mood disturbances, weight gain, osteoporosis, glaucoma	19–45 months
Mitosantrone	Nausea, vomiting, hair loss, amenorrhea, neutropenia, acute myeloid leukemia	12–24 months

3.4. Prevalence of NMO

NMO is a relatively rare disease. Its prevalence ranges from 1/100,000 to 4/100,000 in Europe and North America (Jarius et al., 2014). This means that the experience of neurologists with this disease is necessarily limited. There are few potential research participants, and, therefore, it is difficult to conduct the studies that are needed to provide evidence of therapeutic efficacy and safety. This makes the feasibility of research an important consideration in study design.

3.5. Ethically salient scientific factors

Several of the scientific facts about NMO are ethically salient. Most significantly, NMO is a progressively disabling fatal disease. All of today's patients can be expected to experience additional acute disabling attacks, repeatedly, until death. This means that developing definitive evidence of the efficacy and safety of any relapse prevention therapy is in the long-term interest of every NMO patient.

At the same time, the diagnostic uncertainty of NMO, coupled with the diagnostic use of the biomarker since 2006, undercuts the value of older retrospective studies. Whereas studies from 1977 to 1997 reported that 60% of patients exhibited severe impairment, with new diagnostic tools and criteria, more minor cases can be identified. This makes it especially difficult to compare recently diagnosed patients to historical controls. It also makes it easy to mistakenly conclude that better outcomes in minor cases