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Review article

A review of the ethics of the use of placebo in clinical trials for relapsing-remitting multiple sclerosis therapeutics

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ABSTRACT

Randomized placebo-controlled clinical trials have been considered the most rigorous method of evaluating the efficacy of novel treatment interventions. The first effective disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) were approved in the 1990s after a number of pivotal placebo-controlled trials. Since then, the ethics of the continued use of placebo in clinical trials of new DMTs for RRMS has been the subject of repeated policy statements and recommendations by international committees. As further data have accumulated demonstrating a reduction in long-term morbidity and mortality with early initiation of DMT, a growing consensus has emerged that further inclusion of placebo arms in clinical trials of novel RRMS therapies is no longer ethical.

Contents

1. Introduction

When developing a clinical trial to study the efficacy of a new medical treatment, the first consideration is clinical equipoise: is there a known treatment that has demonstrated superior efficacy to the experimental agent? If a state of ignorance exists about the efficacy of the new agent, a clinical trial may be justified. In the setting of equipoise for an investigational therapy when no established therapy has demonstrated efficacy for the disease being studied, a placebo arm may be ethically justified. The placebo has a long and distinguished role in clinical medicine and research. In controlled clinical trials, inclusion of a placebo arm has been regarded as the most rigorous method to assess the efficacy of putative therapeutic agents. The placebo must be ethically justified and practical. It is ethically justifiable if there is no known effective treatment and practical if its use appears able to produce interpretable results that may answer the question of efficacy. However, once an effective therapy is established, it becomes unethical to treat a human subject with an inferior therapy, such as a placebo, and an alternative trial design, such as an active comparitor, usually is ethically preferable.

In therapeutic trials for the relapsing-remitting phenotype of multiple sclerosis (MS), a placebo arm was essential in the development of effective disease-modifying therapies (DMT). But now that emerging data have demonstrated that DMTs reduce morbidity and mortality in relapsing-remitting multiple sclerosis (RRMS), particularly with early initiation of therapy, a growing consensus holds that it has become unethical to continue to rely on placebo-controlled trials. Alternative clinical trial methodology, such as active comparator superiority studies, may be the most

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suitable replacement for placebo-controlled trials of new RRMS therapies. Here we review the use of placebo-controlled trials (PCTs) in MS and evolving thought on this subject through position papers and published commentary.

2. Placebo use in clinical research trials

In 1801 John Haygarth documented what may have been the first reported placebo-controlled trial (de Craen et al., 1999). Over the following century, physicians experimented with placebo and observed placebo effects while testing various remedies (de Craen et al., 1999). In the early 1900s, the word *placebo* in medical writings began to refer to any inert treatment given concurrently to control subjects in clinical trials (de Craen et al., 1999). Because of the power of the placebo effect, randomized PCTs eventually became considered the most rigorous method of evaluating the efficacy of active treatment interventions. The use of placebo controls has remained controversial, however, because of the need for patient deception (Koshi and Short, 2007). Yet placebos have been widely regarded as ethically acceptable in subjects in whom no proven effective therapy existed for their condition and in which sufficient clinical equipoise was present to test if the treatment under study would be effective (Millum and Grady, 2013). Recent discussions on the ethics of placebo have focused on its use in clinical trials for a disease in which a proven therapy already exists (Avins et al., 2012; Ellenberg and Temple, 2000; Millum and Grady, 2013).

The Declaration of Helsinki, adopted by the World Medical Association in 1964 and updated periodically, is one of the most influential international standards guiding medical research with human subjects (Carlson et al., 2004; Forster et al., 2001; Hellmann et al., 2014; Millum et al., 2013). Its revision in 2000 (Lewis et al., 2002) specifically addressed the ethics of PCTs in an era of available therapy and stating "the risks, benefits, 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" (Lewis et al., 2002). Subsequent revisions over the following decade refined this recommendation culminating in the 2013 update which restricted the use of placebo, no intervention, or an intervention less effective than "best proven therapy" in clinical trials to only those circumstances in which "patients who receive them will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention" (Hellmann et al., 2014; Millum et al., 2013).

3. Placebo-controlled clinical trials of MS therapeutics

Many of the 13 disease modifying therapies (DMTs) currently approved for use in the United States (US) for RRMS were first studied in large phase III PCTs (English and Aloi, 2015; Lublin, 2005; Wingerchuk and Carter, 2014). The first DMTs, interferon beta 1-b, glatiramer acetate, and interferon b-1a, were approved after positive PCTs in the 1990s (Lublin, 2005). Discussions of the ethics of further PCTs in this new era of available therapy for RRMS, as well as an evaluation of potential alternative study designs that complied with the 2000 revision of the Declaration of Helsinki, ensued shortly thereafter (Lublin and Reingold, 2001). In 2000, an international "Task Force on Placebo-Controlled Clinical Trials in Multiple Sclerosis" was constituted to provide guidelines for future clinical trials for MS therapeutics (Lublin and Reingold, 2001). This group concluded that for patients who decline treatment with DMT because of potential side effects of available agents, enrollment in PCTs remained ethical with enhancement of informed consent guidelines. The group further concluded that the participation in PCTs also remained ethical using subjects for whom DMT had "failed" and subjects with progressive MS phenotypes lacking efficacy data for DMT.

The group recognized that PCTs of DMTs in "resource restricted" areas of the world, where access to any DMT was unavailable for financial or political reasons, may be ethically acceptable, providing a stipulation that there would be a reasonable expectation that the study drug, if proven effective, would be made available to the host country after completion of the trial. The group reviewed a variety of alternative study designs, concluding that active comparator studies may not be acceptable to regulatory agencies and studies designed to show superiority of a novel therapy were limited by sample size, outcome measures, and cost (Lublin and Reingold, 2001).

As the development of novel DMTs for RRMS subsequently advanced, the ethics of the use of placebo in clinical trials for these therapies was revisited in meetings in 2004, and 2007 resulting in updated position papers and commentaries in MS-related journals. In 2004, an international panel of experts in MS and clinical trials met under the auspices of the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis to once again consider the ethical challenges of clinical trials of new therapies as a result of the availability of multiple DMTs for MS (McFarland and Reingold, 2005). The group concluded that because DMTs were only partially effective for RRMS and associated with side effects that resulted in compliance challenges, there remained a need to develop new agents.

Acknowledging the ethical concerns surrounding use of PCTs for such agents, the group deliberated the pros and cons of a large number of alternative trial designs but reached no consensus on an optimal alternative. Non-inferiority, equivalency and superiority studies, against available DMTs were considered the most practical means to determine safety and comparative efficacy data between available and emerging therapies. However, the need for a larger sample size and the potential difficulty finding a commercial sponsor for such studies were recognized as challenges. During this time, the first monoclonal antibody to treat RRMS was approved after a pivotal phase III study that included 315 patients who received placebo by intravenous infusion every four weeks for more than two years (Polman et al., 2006).

In 2007, under the auspices of its International Advisory Committee on Clinical Trials of New Agents in MS, the US National MS Society again convened a group to re-examine the ethics of PCTs (Polman et al., 2008). This group concluded that PCTs trials in MS remained ethical, but required additional limitations. They asserted that placebo-controlled trials were ethically justified when the outcomes of placebo therapy "do not increase the risk of serious or irreversible harm". PCTs were also viewed as ethical when subjects with RRMS chose not to take available therapies, with the caveat of carefully specified improvement in informed consent procedures in these situations and emphasis that such trials were not to be presented as an alternative to proven therapies.

To avoid bias and potential patient confusion between clinical care and research, the group also recommended, when possible, to employ separate research physicians to lead the consent process other than the patient's usual treating physician. The group also noted it was permissible to offer enrollment in PCTs to those patients who had "failed" proven therapies, presuming all classes of DMTs had been tried before participation was offered. PCTs or therapies for primary progressive MS and secondary progressive MS were considered ethical because there were no proven therapies for these conditions with the exception of a single therapy for the latter with limited availability in some countries.