Placebo composition as *tabula rasa* in clinical trials.

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INTRODUCTION

Notwithstanding the numerous fallacies and the limitations in interpreting data from the improper application of, and the unquestioned reliance on, statistical models (1, 2), my central question can be stated thus: Can excipients in the placebo modulate pharmacological effect(s) sufficiently so that the differential between (placebo and active) clinical responses could be 'tipped' either in favor of, or against, achieving statistical significance in placebo controlled trials?

Admittedly, not all of the so called 'placebo effects', can be attributed to the pharmacological activity of excipients. For example, the variability in the clinical ratings by trial observers from one site to another, the expectation or anticipation of clinical improvement and consequent increase in endogenous chemicals that cause self-healing responses, empathy, conditioning, beliefs and social cues have all been proven to affect clinical responses (3).

There are, however, some effects that can be attributed to the pharmacological activity of the excipients themselves. Such responses manifest with greater probability in liquid dosage forms, which utilize a broader spectrum of excipients, than in solid dosage forms, where generic 'off-the-shelf' placebos can be utilized.

A phase IIb clinical trial in rheumatoid arthritis patients that utilized a methyladenosine derivative in conjunction with methotrexate in the active arm versus methotrexate in conjunction with polyoxyl 45 castor oil and Miglyol® 812 (caprylic/capric acid triglycerides) as part of the placebo composition, found an equally high number of responders in the placebo arm as those in the active arm (4). It turned out that these excipients upregulated the adenosine receptors A3 and A2A, which are known to attenuate the levels of endogenous inflammatory cytokines (5).

Another placebo controlled trial that utilized mesenchymal stem cells (MSC) for Crohn's disease found an unusually high response rate for patients on the placebo arm. This was attributed to faulty study design (6). The vehicle in which the MSCs' were administered, Plasmalyte A®, consisted of dimethyl sulfoxide (DMSO) and albumin in water. That inflammatory bowel diseases often manifest with an excess generation of free radicals is well documented in the literature along with the ameliorative effects of radical scavengers and antioxidants such as DMSO. It is not incon-

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ceivable that patients on the placebo arm may have benefitted from the inclusion of DMSO in the placebo, although it must be pointed out that placebo administered without deception has been shown to significantly improve symptoms in irritable bowel syndrome as well (7).

Cremophor® EL, a nonionic surfactant and solubilizer present in Taxol®, has been shown to promote cytotoxicity via calcium dependent necrosis in murine models (8), decrease the activity of the P-glycoprotein dependent efflux pump, decrease the accumulation of cisplatin in peripheral blood leucocytes (9) thereby increasing its therapeutic index and to decrease the nephrotoxicity and hepatotoxicity associated with cisplatin in murine models (10). Co-administration of Taxol and cisplatin is therefore expected to lead to a synergistic efficacy increase based on the aforementioned effects of the excipient, Cremophor® EL. Several clinical trials have demonstrated a better outcome for patients with advanced ovarian cancer on the paclitaxel-cisplatin regimen than for those on a cyclophosphamide-cisplatin regimen (11 and references therein).

Tranexamic acid, an antifibrinolytic agent in its own right, is used to solubilize the nonglycosylated form of recombinant tissue plasminogen activator (tPA, a fibrinolytic agent) in Reteplase®. It also retards the binding of tPA to the NMDA receptors by acting as a lysine analog (12). While no placebo controlled trials seem to have been conducted with Reteplase®, the inclusion of an excipient in the placebo which is known to have a diametrically opposite pharmacological effect to the active ingredient can be construed as being conducive to achieving clinical significance, were such a clinical trial to be performed.

It is known that vaccine adjuvants such as alum and MF59® (a squalene-in-water emulsion) have intrinsic immune enhancing properties that act via multiple mechanisms (13, 14). It is also generally recognized that the weaker the antigen, the more is the dependency on adjuvants to provide the innate immune triggering mechanism that elicits effective immunogenicity (15). It can be argued that adjuvants, by themselves, may be incapable of eliciting adaptive immune responses in the absence of dead or weakened pathogens or pathogen proteins. However, where at-risk populations can be clearly defined, there is a greater probability of such antigens already being present in the host (latent period) and thus, the administration of adjuvant alone, may be enough to trigger strong adaptive B and T cell immune responses. In such instances, the contribution of adjuvant that is included in the placebo may be of such a magnitude so as to negate the (real) effect of subunit adjuvanted vaccines (16).

A recent article pointed out that the composition of placebos used in clinical trials is seldom, if ever, disclosed (17). Seemingly innocuous ingredients such as chelating agents, multivalent cations, and preservatives are known to possess intrinsic pharmacological effects with regard to attenuation or amplification of bacterial growth (18). For example, chelating agents, typically present in pharmaceutical formulations as antioxidant or preservative aids, scavenge metal ions which, in some instances, may be essential for the growth of some bacterial populations (19). On the other hand, multivalent cations used as solubilizers or tonicity adjustors may have the opposite effect. Such activity may manifest itself, in conflicting ways, depending upon the mode of administration, concentration and residence time (20, 21). The confounding effects of such ingredients, when present in conjunction with antibacterial APIs' must be carefully considered when designing placebo comparator clinical trials.

Short of identifying a sugar pill being used as a placebo for a diabetes clinical trial, it is very difficult to extract information that is indicative of pharmaceutical excipients, by themselves, functioning to modulate pharmacological responses in placebos. Pharmacological effects can be mediated by 'generic' mechanisms such as the modulation of reactive oxygen species and metal ions or the re-organization or

permeability alteration of cell membrane constituents. These also happen to be the established mechanisms of action for various classes of commonly used excipients. Therefore, even if a part of the 'placebo response' were to be attributed to the pharmacological activity of the excipient, the placebo composition could mean the difference between the trial either crossing the futility boundary or, demonstrating a significant API effect.

Given what we know about pharmaceutical excipients today, it would be very useful to voluntarily disclose the placebo composition used in clinical trials. Such disclosure would not only lend more transparency to the drug approval process, but would also provide reviewers a chance to evaluate whether, and to what extent, excipients in the placebo may contribute toward the outcome. As a corollary, placebo compositions may be designed to minimize any confounding effects with API efficacy. Such compositions, with appropriate justification may, or may not contain all the ingredients that are present in the active formulation. Ostensible improvements in clinical trial design, such as the introduction of the sequential parallel comparison design (22), that specifically aims to reduce the placebo effect, must be carefully scrutinized to ensure that placebo non-responders do not inadvertently constitute subpopulations that are refractory to the excipient(s) mechanism(s) of action(s).

The concept of the placebo as a *tabula rasa*, on which the API's signature is scribed, appears to be an increasingly untenable proposition. Ironically, it may have been made so, in part, because of the increased complexity of emerging excipients used to deliver APIs' to specific pharmacological targets. Many of these excipients possess intrinsic pharmacological activity through well defined mechanisms. Consequently, placebo controlled clinical trials must factor in the excipient bioactivity as well as disclose placebo composition, so that pharmacological responses that are innate only to the API, may be better discriminated.

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