

Editorial

## Output of the working group on magnetic resonance imaging abnormalities and treatment with amyloid-modifying agents

In this issue of *Alzheimer's and Dementia* is a report on the findings of an expert working group regarding vasogenic edema and microhemorrhage (mH), convened in July 2010 by the Alzheimer's Association Research Roundtable (AARR) in response to advice provided by the US Food and Drug Administration (FDA) to sponsors conducting clinical trials with amyloid-lowering agents for the treatment of Alzheimer's disease (AD). The FDA advice addressed concerns regarding potential adverse events, specifically cerebral mH and vasogenic edema, and their relationship to treatment as well as their relationship to each other. Among the FDA's recommendations were: (1) exclusion of patients based on a minimum number of mHs at baseline ( $\geq 2$ ), and (2) discontinuation of patients with any incident mHs during the course of the study. To many clinicians and investigators, the advice appeared stringent and would lead to significant limitations in being able to understand fully the effects of treatment in the typical general AD clinic population in which the treatments would ultimately be used.

Because the advice was issued just before the 2010 Alzheimer's Association International Conference on Alzheimer's Disease, where many key stakeholders were in attendance, an informal meeting was held to discuss concerns regarding the advice. After considering various options, the group decided to use an existing venue for cross-collaboration among industry, academic, nonprofit, and government communities. The AARR was formed in 2003 with the primary mission of helping to facilitate drug development for the treatment of AD. With an antitrust umbrella agreement in place, the AARR has served as an interdisciplinary venue where key stakeholders from across the Alzheimer's community have met regularly to address jointly issues in the field. It was decided that the AARR would urgently convene a work group to review the FDA advice and address the community's concerns.

Working group members from around the globe were identified on the basis of their expertise and interest in the area, regardless of their academic or industry affiliation. The group consisted primarily of neurologists, as well as a neuropathologist, a neuroradiologist, a neurosurgeon, and two neuroscientists, with broad-ranging AD expertise in areas including clinical neurology, clinical trial design

and conduct, neuropathology, and neuroradiology. Members came from across academia, industry, and the nonprofit communities.

The working group's objectives were to: (1) gather and evaluate all relevant, publicly available information including natural history and spontaneous occurrence of these adverse events, particularly in an aging population and in AD; their occurrence in the setting of amyloid-lowering agents for AD; similar clinical conditions from which parallels might be drawn; and existing animal models that could elucidate these phenomena; (2) produce recommendations for inclusion/exclusion and monitoring of participants in clinical trials; and (3) identify potential areas of research that might help increase our understanding of these events. Four work streams were formed to delve into specific areas: (1) cerebral mH, (2) vasogenic edema, (3) pathology of microbleeds and vasogenic edema, and (4) mouse models of microbleeds and vasogenic edema. The subgroups then reconvened as a collective to assimilate and integrate the findings of the individual work streams, to identify areas of consensus and divergence, and to provide recommendations. A neurologist from the FDA also joined the meeting to discuss the group's findings.

The detailed findings and conclusions of the working group are contained in the report published in this issue. They include specific new and revised recommendations for the conduct of clinical trials of amyloid-lowering agents. These recommendations are based on an analysis of all publicly available scientific information on these phenomena, and are the synthesis of these data with the cumulative knowledge, expertise, and collective experience of the group. Particular differences between the original FDA advice and the working group's findings and recommendations are worth noting. In addition to recommendations for reaching technical consistency in acquisition and interpretation of mH, the group concluded that the original FDA advice could be broadened to include more mH cases both at baseline (from two to four) and during the course of the study (from none to allowing some if asymptomatic) without compromising participant safety. These conclusions were based on several factors, including the high prevalence of spontaneously occurring mHs in the population, which are

typically asymptomatic, and were discovered only as incidental findings on magnetic resonance imaging; the lack of information on the clinical significance of mH; limited data to suggest that individuals with mH should be excluded from a clinical trial with an amyloid-modifying agent; and the significant technical variability in acquisition and interpretation of mH on magnetic resonance imaging (with an error rate thought to be  $\pm 2$ ), making it difficult to identify definitively a particular single mH in certain instances. Importantly, broadening the restrictions would allow a better understanding of the potential risks and benefits of amyloid-lowering treatment and would advance the development of treatments for AD without clinical or scientific evidence indicating that doing so would compromise trial participant safety.

In addition to the technical recommendations, the working group considered the terminology of mH and particularly “vasogenic edema” as applied to these phenomena being observed both in the setting of amyloid-modifying treatments as well as in the natural course of AD. Because of the apparent relationship and presumptive related pathophysiology, as well as the various implications of the term “vasogenic edema,” the group decided to use new terminology to describe these phenomena more accurately. The term ARIA was introduced to refer to amyloid-related imaging abnormalities, with ARIA-E referring to the magnetic resonance manifestations of ARIA attributable to vasogenic edema-like occurrences, and ARIA-H referring to the magnetic resonance manifestations of ARIA attributable to mH.

The working group report was sent to the FDA for review and consideration. The FDA subsequently revised and updated the original advice to sponsors in a manner consistent with the report. Specifically, they integrated the aforementioned recommendations along with several others contained in the report published in this issue.

This process that produced the recommendations and the report is an exemplary case of a recent movement in the field

of AD toward collaboration and openness of all stakeholders, regardless of affiliation—academic, industry, advocacy, or government—to advance the process of drug development in AD. This change in the drug development process, to move beyond the goals of the individual stakeholders, comes because of the commitment and relentless efforts of all stakeholders to bring desperately needed treatments to people with AD.

The true value of this important report is a work product that represents the integration of the best expertise and knowledge on the topic, regardless of the affiliations of the individual contributors. It is only the process coupled with the willingness to collaborate that allowed this to be accomplished in such a short time. This process is also a reflection of the ability of an advocacy/nonprofit group to convene a group of top experts, the industry’s willingness to go beyond the proprietary interests of the individual companies, and the openness of the FDA to listen.

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