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Short Communication

Amyloid-Related Imaging Abnormalities (ARIA) in Immunotherapy Trials for Alzheimer's Disease: Need for Prognostic Biomarkers?

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Abstract. At the 8th International Conference on Clinical Trials in Alzheimer's Disease held November 5–7, 2015 in Barcelona, Spain, promising data were presented on two candidate Alzheimer's disease immunotherapeutic agents, gantenerumab and aducanumab. Trial results demonstrated that the implementation of cerebrospinal fluid and Aβ-PET biomarkers improves trial enrichment and outcome, which has led to a change in targeting strategy as clinical trials would be conducted with earlier, even presymptomatic, stages of the disease. Promising findings of outcomes, as measured by Aβ-PET and cerebrospinal fluid tau and P-tau, were, nevertheless, associated with antibody dose-dependent increased risk of severe adverse effects, specifically amyloid-related imaging abnormalities (ARIA). Aducanumab was associated with concomitant time-, dose-, and *APOE*-related incidence of ARIA in more than one-half of the patients within the high-dose arm. The future challenge will thus be to find biomarkers more favorably balanced between effective dosing of antibody to remove Aβ versus dosing to limit deleterious side effects. Interest was shown by Roche and Biogen, which promoted high-dose phase 3 trials. However, this generated some concerns related to a reasonable expected further increase in the incidence of severe side effects. What has been learned is challenging primary industry strategies for following-up and monitoring safety and effectiveness of anti-Aβ antibodies in clinical trials. Here, we debate the issue of what is an acceptable balance of treatment side effects, i.e., therapeutic-induced ARIA, versus the positive prospects. Indeed, implementation of biomarkers for ARIA might increase value and reduce waste in the design of immunotherapy trials of Alzheimer's disease.

Keywords: Aducanumab, adverse effects, Alzheimer's disease, amyloid-related imaging abnormalities, anti-Aβ autoantibodies, cerebral amyloid angiopathy-related inflammation, clinical trial, drug safety biomarkers, gantenerumab, immunotherapy

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INTRODUCTION

In the last decade, the presence of amyloid-related imaging abnormalities (ARIA) has challenged the development of anti-amyloid-β (Aβ) monoclonal antibodies for the treatment of Alzheimer's disease (AD).

The antibody- and dose-dependent ARIA represent a core safety issue, being the main serious adverse events reported in all immunotherapy trials.

Clinically, ARIA presents with relevant neurological signs, while mildly symptomatic or asymptomatic manifestations are usually recognized as incidental ARIA during follow-up evaluation on magnetic resonance imaging (MRI), depending on the pre-planned design of the study.

In order to lower their incidence in clinical trials, the FDA recommended full MRI assessments so as to exclude patients whose imaging exhibited features of ARIA [1, 2]. However, although MRI detects active stages of ARIA, the high occurrence of these adverse events clearly demonstrates that MRI is useless in predicting the risk of developing ARIA during treatment [3].

The strategy of early detection of ARIA received favorable response with the presentation of recent gantenerumab and aducanumab results at the 8th International Conference on Clinical Trials in Alzheimer's Disease (CTAD) held November 5–7, 2015 in Barcelona, Spain [4–9].

Concurrently, exciting new opportunities have also emerged regarding the discovery of new biomarkers of ARIA. The iCAβ International Network [10] reported increased levels of anti-Aβ autoantibodies in cerebrospinal fluid (CSF), and demonstrated that such detection facilitates diagnosis of spontaneous ARIA-like events occurring in cerebral amyloid angiopathy-related inflammation (CAA-ri), which represents a spontaneous variant of the same immunotherapy-induced ARIA [11]. Consistently, as discussed for CAA-ri, the basis to implement the use of CSF anti-Aβ autoantibodies as candidate biomarkers of ARIA assumes a relevant finding from gantenerumab and aducanumab trials, especially considering the fully human origin of these two anti-Aβ monoclonal antibodies [3, 11, 12].

DISCUSSION

At the CTAD, aside from cautious optimism that anti-amyloid immunotherapies might actually be working, we raised concerns about the difficulties to avoid ARIA side effects [4–9, 11].

The challenge to managing ARIA is underscored by the latest results of gantenerumab and aducanumab studies, two of the most promising investigational immunotherapies in sporadic AD.

Following gantenerumab Phase 3 SCarlet RoAD (NCT01224106; WN25203) trial interruption in December 2014, for pre-planned futility analysis, Roche presented new *post hoc* analyses of the clinical efficacy and safety data of the 2-year follow-up population of completers. Of note, based on the lessons learned from Phase 1, and in an attempt to mitigate the risk of ARIA, although these patients were treated either with 105 mg or 225 mg of gantenerumab depending on their *APOE ε4* status, a surprisingly high occurrence of ARIA emerged for both arms, with overall incidences of 12 and 15%, respectively. The *post hoc* analysis also showed dose-dependent beneficial trends on clinical decline and on CSF P-tau, T-tau, and Aβ-PET. Benefits were more evident for *APOE ε4* non-carriers treated at the higher (and more effective) dose, compared to carriers. Taken together, these new findings led Roche to re-interpret the SCarlet RoAD failure as a result due to a sub-optimal therapeutic dose of gantenerumab, supporting the movement toward new exploratory, high-dose trial strategy.

Of note, all the data had been obtained from a well-selected screening of the original SCarlet RoAD whole population of patients, which excluded cases with levels of CSF $A\beta_{42}$ above the predefined cut-off for AD. This is extremely important because it means that biomarker screening for baseline-positive Aβ may lead to better trial outcomes. Conversely, these data also imply that the next Phase 3 trial at higher doses of gantenerumab, even if in well-selected Aβ-positive patients in prodromal AD stages, might further increase the incidence of ARIA, particularly in *APOE ε4* carriers [4, 5, 9].

More could be learned from the Phase 1b, interim analysis of the PRIME study with aducanumab (NCT01677572). Biogen reported that aducanumab significantly slows cognitive decline, and is associated with a dose- and time-dependent lowering of Aβ-plaque burden on PET. It is worth of note that, for the first time, PRIME was conducted in a well-selected population of baseline Aβ-PET positive patients with prodromal or mild AD, randomized to receive aducanumab at 1, 3, 6, or 10 mg/kg within different treatment arms stratified by *APOE ε4* status. Consistent with the gantenerumab findings,

aducanumab was associated with a dose-dependent dramatic increase in the incidence of ARIA, rising from 7% in the 1 mg/kg arm to 55% in the high-dose arm, mostly in *APOE* ε4 carriers [6–8].

Taken together, the message from the Phase 3 trials of gantenerumab and aducanumab reveal that the challenge is to manage the ARIA side effects, in order to enable amyloid clearance without harming the patient. This represents a timely issue, considering the large number of patients who discontinued the treatment due to the development of ARIA [3].

The iCAβ International Network [10] recognizes that spontaneous ARIA-like abnormalities also occur in CAA-ri [11]. Increase in CSF anti-Aβ autoantibodies is a key to manifestation of ARIA, causing a shift in CAA accumulation and increased vascular permeability that eventually leads to vascular leakage and inflammatory events at the sites of greater Aβ removal [3, 11, 13–17]. In fact, in line with immunotherapy, high levels of anti-Aβ autoantibodies in CAA-ri have been associated with a massive release of soluble Aβ from plaques and vascular deposits during the acute inflammatory phase, which is followed by reduced levels of the neurodegenerative markers tau, P-tau [13, 15] and Aβ-PET [16, 17] after clinical and radiological remission of the disease.

Taken together, such evidence point to the promising role of CSF anti-Aβ autoantibodies as biomarker for the monitoring of ARIA [3].

Noteworthy, ARIA-like abnormalities are found in other populations, including: untreated, prodromal AD with and without identifiable underlying CAA; cognitively normal elderly; and familial AD (FAD). This has important implications for the recently launched ponezumab (NCT01821118) trial in sporadic CAA and for the DIAN-TU (NCT01760005) and crenezumab (NCT01998841, NCT02353598) studies in FAD (for references, see review [3].)

To deal with these challenges, an acceptable plan in immunotherapy trials would be to determine anti-Aβ antibodies concentration levels in CSF following dosing of therapeutics in order to determine biomarker criterion levels that would be used to stratify patients and personalize treatment for greater clinical effect while minimizing putative side effects, particularly in patients at high risk for ARIA (i.e., with high CSF autoantibody titer at the baseline and/or carrying *APOE ε4* alleles). This may perhaps explain the failure of previous trials, where ARIA concerns led to limiting the dose of drug administered [3]. Of relevance, in the unlikely occurrence of ARIA, such biomarker will allow a prompt inclusion in an opportune treatment protocol, e.g., steroid administration as efficiently demonstrated in CAA-ri [13, 14], thus avoiding the exclusion of these patients from the trial [3].

SUMMARY

The lack of specific biomarkers for ARIA is a serious challenge to the design of immunotherapy trials that could lead to unacceptable delays.

Recent evidence presented at the CTAD Barcelona meeting, both from Academia and Industry, gave new hope to promising candidate biomarkers. The data on gantenerumab [4, 5, 9], aducanumab [6, 7, 8] and naturally produced anti-Aβ autoantibodies [11], in particular, seem to suggest an etiological model for ARIA that we can call "The ARIA Paradox". In such a model, a rapid increase of CSF anti-Aβ antibodies (both therapeutically administered and/or spontaneously produced) explains a detrimental but transient loop, in which the physiological pathways of Aβ clearance may get saturated by the massive removal of deposited Aβ by antibodies, particularly in patients with high degrees of cerebrovascular-deposited Aβ [3].

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