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Letter – Expert Discussion

Anti-amyloid treatments, a therapeutic revolution, ready for Europe

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Text

On 9th October 2025, the Cognitive Neurology Platform of the Lausanne University Hospital's Department of Clinical Neurosciences organized its 2nd Annual Symposium, together with the Swiss Memory Clinics, the Swiss Society of Neurology, the Swiss Professional Society of Geriatric Medicine, and the Swiss Society of Psychotherapy of the Elderly. This symposium hosted local and international speakers to discuss the biological, ethical and economical dimensions related to the therapeutical revolution of anti-amyloid immunotherapy for Alzheimer's Disease (AD) patients, after the successful phase III RCT Clarity AD [1] and TRAILBLAZER-ALZ 2 [2]. Interestingly, this symposium happened between the two contrasting decisions from European's Medicines Agency (EMA) on lecanemab, namely its initial refusal (25th July 2024) and its marketing authorization (14th November) [3].

Olivier Rouaud opened the meeting with a comparing the FDA approval of zidovudine for acquired immunodeficiency syndrome (AIDS) in 1987, the year the first APP gene mutation was discovered [4], and lecanemab approval.
« We are dealing with an unusual disease, and society has to meet the challenge of handling it in new and innovative ways. There are high public expectations for a drug such as zidovudine. Unfortunately, we know that it does not cure AIDS. I sincerely hope that zidovudine is only the first of many agents that will prove to be valuable in the treatment of AIDS. But only if we exercise restraint in the use of zidovudine, can we expect to learn more about it and do more good than harm. Meanwhile, medical research continues toward the goal of controlling this deadly disease ». Replacing zidovudine and AIDS with lecanemab and Alzheimer's disease, history seems to be repeating itself.

Below, we present the principal thoughts and messages of the experts who contributed to this Symposium in a question-and-answer style. The opinions expressed are those of the experts and not necessarily a consensus shared by the panel.

Paolo Salvioni Chiabotti: did you expect such a quick turnaround from EMA? Are you surprised by the data advanced in their press release excluding ApoE4 homozygous patients [3]?
Federica Agosta: given the complexity of regulatory processes, the EMA's relatively quick turnaround is remarkable but not entirely unexpected, considering the urgency of introducing new therapeutic options for AD. A delay in approval could have created a significant disparity, leaving Europe behind other regions. Despite the necessary caution, lecanemab has demonstrated both clinical and, more importantly, biological efficacy, marking the beginning of a new era in AD treatment. Rejecting it would have posed significant ethical and scientific challenges, potentially hindering progress in the field.
Regarding the exclusion of ApoE4 homozygous patients, the data present a complex picture. Clinical trials have shown that ApoE4 homozygous carriers treated with lecanemab exhibited a significantly higher risk of amyloid-related imaging abnormalities (ARIA), particularly edema (ARIA-E), namely 32.6%, compared to 10.9% in heterozygous carriers and 5.4% in non-carriers. Interestingly, since ARIA is a direct consequence of amyloid removal, one might expect improved clinical outcomes with amyloid burden reduction. However, clinical efficacy appears to be lower in ApoE4 homozygous patients. Post-hoc analyses of trial data are essential to investigate not only the higher incidence of side effects but also to better understand the reduced efficacy in this group. One possible explanation is that the disease in these patients is at a more advanced biological stage, or that the treatment duration in the trials was insufficient to fully address disease progression. I strongly believe that further studies are necessary to explore potential therapeutic opportunities for these patients and to refine our understanding of how to optimize treatment for them in the future.
Fabrizio Piazza: In my opinion, EMA's re-considerations are sensible and in line with the global scenario that see global approval of anti-amyloid treatments (AAT); while, on the other hand, the non-approval of such drugs would have meant excluding EU patients and EU science from entering into a new era in AD treatment. With the EMA approval of lecanemab, and reasonably also of donanemab in the very next months, EU and EU patients will finally have the opportunity to keep pace with the rest of the world.
Regarding the decision of excluding homozygous ApoE4 patients, I believe this is not the optimal solution at long term, because of intrinsic ethical considerations (such as limiting the opportunity of personal

therapeutic decisions of the broad AD community). We must however acknowledge that current evidence on the mechanisms and significance of ARIA is scanty, and more research effort is needed. In this framework, I think that the decision is in line with an intial conservative approach, waiting for clearer data that will emerge from real-world clinical practice. To this end, there is hope that these limitations are transient, and that the use of AAT will be also open to CAA and homozygotic ApoE4 patients in the near future. To accelerate the path, investments in biomarker research will be key since MRI alone demonstrated poor capacity in predicting ARIA as well as in decision making for continued dosing in the case of asymptomatic ARIA-E index events. In the best-case scenario, new MRI markers will improve early diagnosis of ARIA [5]. Fluid biomarkers, instead, may be a game changer for the future of AAT, improving patient selection based on risk stratification, drug-dose monitoring with companion diagnostic biomarkers and ARIA prediction [6], [7], [8], [9].

Paolo Salvioni Chiabotti: In both phase III RCT, a substantial proportion of placebo-treated patients developed ARIA-hemosiderosis/microhemorrhages (ARIA-H) , although to a lesser extent than treated patients. Does this imply that ARIA-H actually is a natural phenomenon in AD, unmasked and decompensated by AAT?
Federica Agosta: the presence of ARIA-H in a substantial proportion of placebo-treated patients suggests that cerebral microbleeds and hemosiderosis may be intrinsic to the pathophysiology of AD, rather than solely a consequence of AAT. This aligns with the well-established association between amyloid pathology, particularly cerebral amyloid angiopathy (CAA), and microvascular fragility. CAA leads to the progressive deposition of amyloid in vessel walls, predisposing them to spontaneous rupture and hemorrhagic events. However, the fact that ARIA-H occurs more frequently in treated patients indicates that AAT can exacerbate an underlying process rather than create a novel pathology. The amyloid clearance hypothesis suggests that removing amyloid plaques from the brain may destabilize vessel walls already compromised by CAA, leading to an increased risk of microhemorrhages. Additionally, the role of genetic predisposition, particularly ApoE4 carriership, further supports the idea that some patients are inherently more vulnerable to cerebrovascular complications.
Emerging evidence also suggests that plasma biomarkers such as p-tau217 are associated with increased amyloid burden and a higher number of microbleeds [10], highlighting their potential utility in identifying individuals at greater risk of CAA-related complications. Validating such biomarkers will be crucial to stratify patients based on CAA severity and optimize treatment strategies.
Ultimately, while ARIA-H may be an unmasking and decompensation of an existing pathological process rather than a direct consequence of AAT, further longitudinal studies are essential to disentangle its natural trajectory in AD from treatment-related effects. A better understanding of these mechanisms will be critical for refining patient selection, optimizing treatment strategies, and minimizing risks associated with AAT
Fabrizio Piazza: The last 10 years of research and experience from CAA-related inflammation (CAA-ri) and the inflammatory Cerebral Amyloid Angiopathy and Alzheimer's disease Biomarkers International Network (iCAβ) have provided robust evidence that ARIA in clinical trials is the iatrogenic manifestation of CAA-ri. There is increased consensus that CAA-ri represents a human spontaneous model of ARIA and more globally of AAT in AD. In this framework, the quantification of both monoclonal antibodies and spontaneous auto-antibodies against amyloid beta peptides may represent biomarkers of ARIA, with the potential to qualify for a companion diagnostic biomarker for drug dosing and monitoring in order to maximize effects while preventing ARIA's occurrence or progression [7], [8], [9], [11], [12], [13], [14].
Giulia Bommarito: In my opinion, we should differentiate between ARIA-H occurring with ARIA-E and isolated ARIA-H. In Clarity AD [1] , 17.3% and 9.0% of patients under treatment or placebo, respectively, developed ARIA-H, while in TRAILBLAZER-ALZ 2 [2], ARIA-H were detected in 31.4% and 13.6% of patients under treatment or placebo, respectively. However, isolated ARIA-H (without ARIA-E) in Clarity AD trial were reported in 8.9% and 7.8% of patients under treatment or placebo, respectively. A previous study described new microbleeds in 12% of patients from a memory clinic over a period of follow-up of 1.9 years [15], while the mean incidence of MB in patients with AD has been reported as 0.7/year [16]. While the mechanism underlying ARIA-E is likely to be inflammatory and clinic-radiological manifestation resemble CAA-ri, ARIA-H, when isolated, might represent the progression of a comorbid CAA in patients with AD, and could therefore be expected along the trial observation period. However, AAT possibly accelerate CAA progression or vascular damage due to amyloid deposits. This might occur through different mechanisms: the increased

trafficking along perivascular spaces or the antibody-mediated blood-brain barrier disruption occurring after immunization [17]. The exact mechanisms underlying both ARIA-H and ARIA-E during AAT deserve further investigation.

Paolo Salvioni Chiabotti: in parallel to the positive results of the two-phase III trials in AD (namely Clarity AD and TRAILBLAZER-ALZ 2), a substantial portion of the AD community interrogates itself about the concept of clinical meaningfulness. How should clinicians judge it whether the primary and secondary outcomes of these trials are relevant to patients? Given the intrinsic nature of interindividual variability in neurological diseases, is the concept of clinical meaningfulness ethically acceptable?
Philippe Ryvlin: While meaningful for homogenous populations, this concept is not meaningful for heterogeneous populations. From a practical point of view, one should examine the data to see whether there is evidence of sub-populations for whom the benefit reaches a threshold considered clinically meaningful.
Giovanni B. Frisoni: First, variability and heterogeneity are not typical of neurological diseases. The process of diagnosis-prognosis-treatment typical of all branches of Western medicine aims to narrow down phenotypic variability. As a scientist, I can accept a 25% average slope reduction as a clinical trial results. However, as a clinician I am much more interested in other metrics of efficacy. For instance, how many long-term non-progressors do we have in the treated group that we do not have with placebo? Statistically, this is a number needed to treat metric, which is much more meaningful to clinicians, who do not treat "the average patient", but that one specific patient. The number needed to treat of monoclonal antibodies has not been explicitly provided in Clarity AD and TRAILBLAZER-ALZ 2 trials, but can be easily computed between 10 and 13, of similar magnitude if not better than other biologics in cancer and multiple sclerosis.
Ralf J. Jox: From an ethical point of view, any therapeutic agent that is authorized for clinical use should have a clear net benefit for the patient population, ideally an added benefit compared to the existing therapeutic options. This is also required by professional medical ethics according to the obligations of beneficence and non-maleficence. This net benefit should be evidence-based on the population (statistical) level. In order to demonstrate net benefit, objective and subjective measures can and should be employed. With fine-grained objective measurements, sometimes a benefit can be seen that is not confirmed by subjective measurement, i.e. it is not clinically meaningful. In my view, clinical meaningfulness is key. Therefore, clinical trials should ideally include measurement of (patient-reported) quality of life. This usually also requires that the beneficial effect is sustained and not only short-lasting. Regarding these two trials I have doubts regarding the clinical meaningfulness of the benefits. Positive outcomes on the patient's family or on the progress of scientific research are not sufficient to justify authorization of a new drug in the regular market. In such circumstances, it would be ethically favorable to do more, better designed clinical trials (in larger populations, for a longer period, with more relevant outcome parameters). Last, the concept of net benefit in a clinically meaningful way requires balancing benefits with risks and burdens. While the risks of ARIA may be considered limited (as it is often not clinically perceptible), the burden of treatment is still considerable (infusions at the hospital, surveillance exams), which, in my eyes, underscores the preference for more studies before authorization, at least for a broad patient population (maybe authorization for specific subpopulation maybe be more proportionate).

Paolo Salvioni Chiabotti: treating patients with AAT means conscientiously informing patients and families, preparing infrastructures (for treatment administration, clinical and radiological follow-up), and teaching physicians (with a particular focus on stroke neurologists, radiologists, and emergency physicians). Do you think that given the relatively small number of eligible patients; such investments are necessary to avoid serious adverse events?
Ralf J. Jox: Safety is a key principle in clinical medicine and in the authorization of new drugs. Surveillance is one way to promote safety. The less robust clinical trial data are, the more questionable the benefit-risk balance is and the more deleterious a breach of safety would be (e.g. retraction of the new drug for a prevalent disease like AD in the context of extreme hopes), the more important are these safety measures. At the same time, safety measures do not depend on the size of the patient population because each patient has inalienable human rights and should be protected irrespective of whether his or her clinical situation is prevalent or not. Post-marketing surveillance to identify serious adverse events is therefore important in the case of these new drugs, even if authorized for a small sample. – If safety and its surveillance depend on

teaching of physicians, this should also be ensured. – Informed consent by patients and (in the case of lack of decision-making capacity) their family surrogates are also a key ethical principle. The more questionable the net benefit is, and the more difficult trial data are to understand, the more emphasis should be placed on good information. We should also stress here that any clinical information to obtain consent should always be tailored to the situation of the patient population: in the case of AD, especially if cognitive deficits are already relevant, information should be provided in a way that the patient actually understands and allows him to make an informed, autonomous choice without being coerced or manipulated.
Simon Wieser: These safety investments are essential when introducing a new treatment, not only to safeguard patient health but also to foster public confidence in the clinicians administering a new and controversially debated therapy. Moreover, they will play a crucial role in evaluating the safety and effectiveness of AATs within real-world treatment settings.
Patrik Michel: For any new treatments, the medical community has an obligation to anticipate, prepare, inform, and educate patients, next of kin and caregivers about potential side effects. This will allow physicians to better identify patients at risk, but also to make better treatment decisions once side effects occur. It is true that an important safety surveillance program with important logistics is required for the small proportion of AD patients who are AAT-eligible. However, this can be considered a "run-in phase" where physicians will be particularly vigilant about side effects. Such an approach will benefit future patients once treatment indications will widen and new drugs will become available. Hopefully, such future AAT regimens will have an event more favorable benefit-risk ratio, so that education and surveillance protocols can become lighter, patient-friendlier, and economically more interesting.
Giovanni B. Frisoni: indeed, the volumes will not represent a deluge, at least in the early times. However, was the system prepared when the first biologics were introduced for multiple sclerosis? Were infusion centers already set up? Were MRI slots for treatment follow-up reserved in advance? Of course not, the different components of the system were gradually put in place after the drugs were introduced, and the system gradually adjusted to the volumes of the patients as biologics gained steam.
Beatrice Pizzarotti: Preparation and information are key for introducing a new treatment in current medical practice in the best possible way. The potential AAT-eligible patients are a small fraction of all AD patients. Nonetheless, AAT might change the way the disease itself is seen by the medical community. The actual identifiable obstacle is censorship, i.e. not referring patients to memory clinics because AD is not treatable. By the same principle, patients and/or next of kin might banalize the first cognitive signs, considering them secondary to "normal aging". Proper information and sensibilization of general practitioners, patients, and families about AD and AAT could change the number of patients referred for AD in memory clinics and, consequently, the effective number of eligible patients. Second, the expectations are high, so patients and families had to be properly informed about the expected benefits, the treatment implications (repeated perfusions and cautious follow-up), and the warning signs for complications. This step is crucial for early adverse events detection. Finally, since AAT complications are potentially lethal and partially preventable, their management demands proper preparation, investment, and information to the different physicians. Moreover, since ER is not the usual setting where AD patients are evaluated, to avoid misdiagnoses and improper treatment, suitable protocols must be implemented and physicians promptly informed.

Paolo Salvioni Chiabotti : predictions of the number of patients suffering from dementia all point to an increase. This seems to vary from country to country, with Europe being no exception [18]. Do you think that implementing AAT with their impact on direct and indirect healthcare costs is realistic? Is it possible to accurately estimate costs and savings as suggested by some authors [19] ?
Simon Wieser: While the costs of treatment and monitoring per patient are relatively straightforward to estimate, assessing the potential savings is far more complex. Savings in direct medical costs of dementia are primarily driven by delayed nursing home admissions, whereas saving direct non-medical costs mainly impact family caregivers. Therefore, estimating potential savings hinges on accurately predicting the effectiveness of AAT in slowing disease progression. Crucially, this effectiveness will depend on the ability to identify and select patients most likely to respond positively to the treatment.
Philippe Ryvlin: Given the intrinsic costs of treatment and monitoring, I can hardly imagine that AAT proves cost beneficial. Nevertheless, I can assume that in a given country, one can model its economic impact and therefore predict its cost-effectiveness.

Giulia Bommarito: Currently, AAT are a reality in several countries, all over the world, with various health systems. Implementing these treatments is possible with an accurate modeling of the different impact they would have, based on each country health system. The availability of more precise and accessible biomarkers, as emergent blood biomarkers, could help selecting patients who would benefit more for these treatments, gaining in benefit-risk balance and reducing the occurrence of side effects. The implementation of AAT in African and Middle-East countries, where dementia rate is expected to increase most [18], is particularly challenging. Special care should be taken to prevent the creation of socio-economic disparities when implementing AAT.

Paolo Salvioni Chiabotti: given the uncertainty surrounding potential side effects, particularly in relation to common neurological comorbidities in AAT-eligible patients like stroke or epilepsy, how should the healthcare system prepare to manage these comorbidities, especially in emergency situations?
Philippe Ryvlin: Serious side effects are common in novel therapies in several fields (e.g. oncology, neuro-immunology), and the healthcare system is usually resilient to such emerging issues. I therefore don't foresee here a critical concern.
Giovanni B. Frisoni: In Switzerland a task force has debated this issue at length and has come out with a set of recommendation that call for education among all the main actors (neurologists, emergency physicians, interventional neuroradiologists, general practitioners, dementia specialists…) about the potential adverse events, what to do and not to do, and, most importantly, transparent and effective communication among all actors.
Patrik Michel: The medical community will have to prepare in two ways for such acute neurological events, spontaneous or as a side effect of AAT: first, AAT-centers will have to anticipate them and prepare specific operating procedure how to treat such double pathologies. Second, these centers should enter such patients into prospectively constructed registries that will allow as systematic evaluation of such double pathologies and/or double treatments in the "real world" setting. This will allow better identifications of AAT-patients at risk for acute neurological events and educate us about best treatment options.
Beatrice Pizzarotti: Preparation and anticipation are crucial to address this issue. For this reason, appropriate recommendations based on the results of the main trials have been established on a national level. It is important to highlight that not only memory clinics are the main partners, but also ER and neurology units. Since the last two units are not often unfamiliar with AD patients' management, open discussion and proper teaching are mandatory to prepare for side effects, comorbidities identification and management. Despite the efforts and thoughtful preparation, there is still plenty of information that we do not know about AAT proper management (e.g. the bleeding risk for patients under AAT who undergo i.v. thrombolysis). For this reason, dialogue and interplay between the different health care partners is not only necessary in the preparation phase, but should be perpetual to improve our knowledge on AAT complications and improve medical practice. With this purpose in mind, local and national registries to collect data about AAT side effects will play a central part.

Conflict of Interest Statement
The authors have no conflicts of interest to declare with regards to this discussion. Prof. Gilles Allali was a member of the journal's Editorial Board at the time of submission.

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