Industry and Academia Partnering to Advance Prevention and Treatment of Alzheimer's Disease

PEER REVIEWED

According to current evidence, Alzheimer's disease (AD) is a disease continuum with a 10-20-year pre-symptomatic phase preceding the onset of dementia. The International Working Group (IWG) on research diagnostic criteria for AD provided in 2007 a new framework where the presence of biomarkers characteristic of AD, albeit not mandatory for diagnosis, provides additional proof of diagnosis in the absence of clear clinical manifestations. Subsequently, the National Institute on Aging - Alzheimer´s Association (NIA-AA) adopted similar diagnostic criteria anchored to temporal order of changes in biomarkers. Both sets of criteria define three stages in AD: preclinical AD, mild cognitive impairment (MCI) due to AD (NIA-AA) or prodromal AD (IWG) and AD dementia.

Although the paradigm of developing medicinal products for the symptomatic treatment of mild to severe AD dementia remains an important and active research field, the focus of development programmes has shifted towards evaluation of new treatments in earlier disease stages. This shift has been appropriately picked up by regulatory authorities in the ICH regions. According to the Workshop on Alzheimer's disease arranged by EMA in November 2014[1], with representation from European regulatory authorities, Japan (PMDA), the US FDA, academia and patient organisations, current regulatory thinking would seem to be sufficiently harmonised to support global development programmes in earlier stages of AD. This workshop is part of the process[2], which in Europe is expected to result in revision of the relevant CHMP Guideline[3].

In the past 15 years, despite a considerable level of investment, the failure rate of clinical development programmes intended to bring new medicinal product to the market for the treatment of AD has been very high. According to a recently conducted analysis[4], in the period between the years 2002 and 2012, 244 compounds were studied in 413 trials for AD. Of the new candidates, which were advanced to Phase III and completed this development stage, only one made it to the market in the EU and the US. This resulted in a 99.6 % failure rate when compounds which were in Phase III at the time of survey were excluded.

The current AD treatment pipeline remains modest. The largest number of trials has been conducted to evaluate efficacy and safety of new compounds intended to slow down the disease process (53.5 %), followed by compounds intended to provide symptomatic improvement (36.5 %)[4]. Most of the studied therapies with disease-modifying intent have targeted Amyloid β, followed by neuroprotective approaches and tau-related mechanisms.

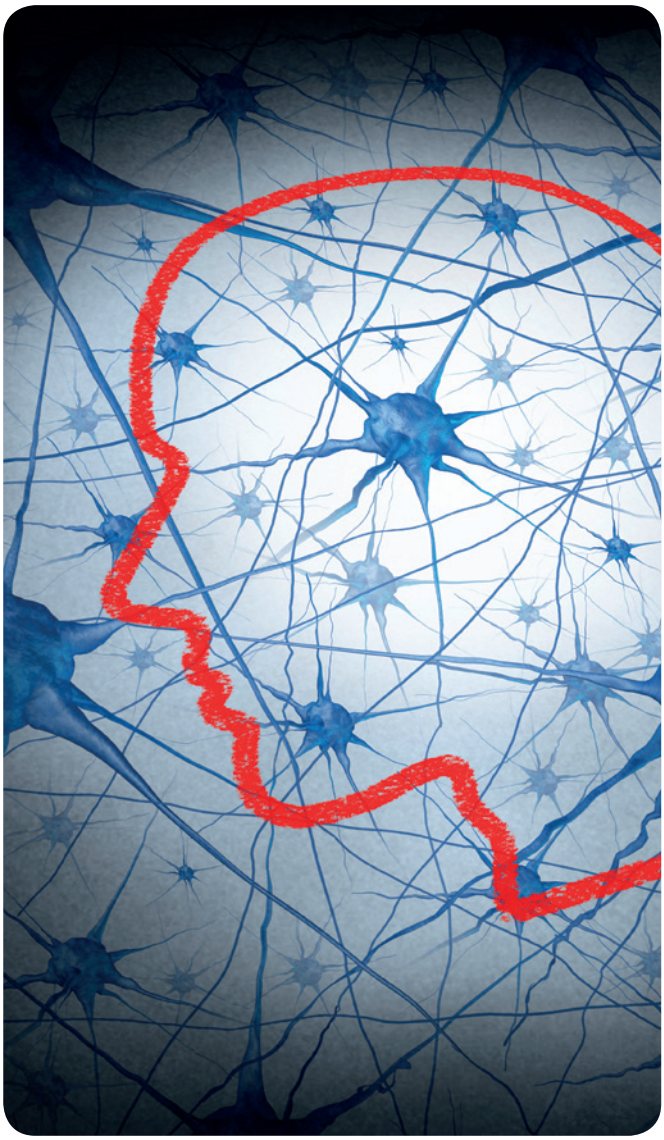
Hitherto, none of the putative disease-modifying therapies have delivered conclusive evidence of clinical efficacy in confirmatory trials despite promising results in non-clinical models and possibly early clinical trials to evaluate biomarker effects. A number of reasons for these failures have been raised for speculation, including selection of study populations and unexpected results in placebo groups. The possibility remains that for disease-modifying effect, combination treatments targeting several pathophysiological processes of AD concurrently will be required.

Prevention of AD is among the most challenging research targets. In the absence of studies, it has not been possible to give any detailed regulatory guidance on this topic. According to the EMA/CHMP discussion paper[2], prevention trials are based on the assumption that patients with pre-clinical AD can be treated with multi-domain interventions, or known safe drugs or new pharmacological targets. Efficacy is demonstrated using time to onset of cognitive impairment or time to onset of dementia as endpoints. Prevention trials require large samples and long follow-up, typically of at least five years. Clearly, major research efforts will be needed to establish preliminary proof-of-concept to select treatment candidates for confirmatory trials in AD prevention.

Recently, very significant advances have been made in organising and structuring research efforts to develop knowledge base and new approaches to prevention and treatment of AD at national, European and global levels, bringing together the different stakeholders, their expertise, experience, research platforms and access to patients and people at risk of developing AD dementia. In Europe, the Innovative Medicines Initiative (IMI) Alzheimer's Disease Platform currently entails three substantial projects: AETIONOMY, EMIF and EPAD. These activities are mainly sponsored by the European Commission and the European pharmaceutical industry (via EFPIA) under the auspices of the Innovative Medicines Initiative Joint Undertaking (IMI JU).

The AETIONOMY project[5] aims at organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy with a view to improving opportunities to targeted treatment. Available and emerging knowledge from molecular data to symptoms will be used to construct a new classification of patient groups based on the underlying causes of disease.

The European Medical Information Framework (EMIF)[6] project has been set to develop a common information framework that will facilitate access to existing diverse and fragmented medical and research data sources, ease



the creation of links between sources and, where needed, collect additional information. The work will address issues such as data standards, semantic interoperability, ethics, data privacy, legal issues, and the development of an IT platform that allows access to multiple data sources.

The European Prevention of Alzheimer's dementia (EPAD)[7] project is a collaborative research initiative to improve the chances of preventing Alzheimer's dementia and to better understand early aspects of Alzheimer's disease before dementia develops. EPAD will establish a European-wide register of 24,000 participants, of which 1500 will be invited to participate in a trial to test new treatments for prevention of Alzheimer's dementia. Longitudinal follow-up of approximately 6000 participants is planned. The clinical trial platform will enable the conduct of adaptive, multi-arm, multi-centre proof-of-concept studies with a view to efficiently identifying candidate compounds or combinations to be taken forward to confirmatory trials. Participants entering these trials will have been identified as being at risk of developing AD dementia based on biomarker evidence consistent with AD.

These IMI projects will work closely with other related research initiatives, such as the UK Dementias Platform developed and led by the Medical Research Council[8] and the Global Alzheimer's Platform (GAP)[9]. In March 2015, GAP and IMI announced that they will sign a memorandum of understanding to accelerate development treatments for AD by building a global, standing, trial-ready platform. The collaboration will work together to recruit patients for clinical trials, to create a high-performing clinical trial system, and to develop a standing adaptive protocol to test new molecules quickly, and move those with promise into later-stage development[10].

These ongoing and novel collaborations hold promise that effective preventive and treatment measures could be found and appropriately targeted to achieve best benefit-risk balance, and that the discouragingly high failure rate in confirmatory clinical development stage may be diminished.

References

1. Workshop on Alzheimer's disease, 24-25 November 2014, EMA/180375/2014
2. Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias. EMA/CHMP/539931/2014
3. Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias. EMA/CHMP/617734/2013
4. Cummings et al. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimer's Research & Therapy 2014, 6:37
5. www.aetionomy.eu
6. www.emif.eu
7. EPAD Master Press Release, Final.
8. www.mrc.ac.uk/research/facilities/dementias-platform-uk/
9. www.ceoalzheimersinitiative.org
10. www.ceoalzheimersinitiative.org/global-alzheimer%E2%80%99s-platform-and-innovative-medicines-initiative-sign-memorandum-understanding

Markku Toivonen, MD, PhD - Former CPMP/CHMP member for Finland, chairman of CHMP Scientific Advice Working Party and CPMP ad hoc group on pre-clinical comparability of biotech products, member of CPMP Blood Products Working Group. Markku has over 20 years' expertise in regulatory affairs, including assessment of non-clinical and clinical dossiers of marketing authorisation applications for small chemical entities and recombinant biotherapeutics. He is currently a member of NDA Group's Advisory Board.
Email: info@ndareg.com