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Brief Report & Presentations

2ND WORKSHOP ON NEURODEGENERATIVE DISEASES: FOCUS ON DEMENTIA

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Overview. Michael Donaghy, Department of Clinical Neurology, Oxford University, UK

With the imminence of therapies to alter the underlying natural history of dementia of the Alzheimer's type, this workshop sought to summarise our current ability to evaluate treatment outcomes. The workshop provoked lively discussion, and was well attended by a number of European and North American experts in the field, representatives from the pharmaceutical industry and patient organisations, as well as the EMEA and members of its Clinical Neurosciences Scientific Advisory Group.

Of particular importance was the consideration of measuring outcomes, with the acknowledged need that clinical endpoints remain of crucial importance, although these will need to be increasingly benchmarked against biological outcome markers, including serial volumetric magnetic resonance imaging (MRI).

Important discussions addressed the increasing heterogeneity of the dementias and the question of whether any one treatment could provide universal benefit across a range of dementia syndromes. A view emerged that pharmacological interventions which intervened at a late stage in the pathogenic pathway, and were therefore likely to be applicable to a range of dementia syndromes in large numbers of patients, would certainly need to be assessed against clinical outcome measures.

However, interventions aimed at early points in pathogenetic pathways would be aimed at smaller subsets of biologically-defined patients, without the possibility of performing clinical trials large enough to produce conventional statistical outcomes; in this setting biological outcome parameters (biomarkers) were considered to be a particularly important development for evaluating such interventions.

Neuroimaging in trials in Alzheimer's dementia. Nick Fox, Institute of Neurology, University College London, UK

Alzheimer's disease (AD), the commonest cause of cognitive decline and dementia, is one of the most devastating healthcare problems facing Europe with its ageing populations. For the individual dementia is one of the most feared risks of ageing; for families and carers the burden is devastating, with individuals spending several years needing full-time care. Already dementia costs the health and social care economy of Europe more than cancer and heart disease combined. Increasing longevity combined with an exponential relationship between age and prevalence of AD means that the numbers of sufferers with AD are likely to grow rapidly in the coming decades. Current therapies offer, at best, modest symptomatic benefit. There is a critical need now to improve treatments and to show sustained effect. The ultimate aim, and the focus of major pharmaceutical effort, is to find treatments that delay

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)7 418 8613
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

onset or truly slow progression; ideally with effective disease-modifying therapy that can be delivered at the prodromal stage (prior to the clinical manifestation of the disease).

There are many candidate treatments currently being developed with the aim of slowing progression of disease. There are a number of key areas where imaging may contribute to this aim. These include how to define and enrich the target population and to assess safety and efficacy.

1. Diagnostic markers for AD – to add support to a clinical diagnosis of AD – structural imaging (especially MRI) functional imaging and more recently molecular amyloid imaging have proven value.

2. Predictive markers – to predict risk of progression from a pre-AD stage e.g. mild cognitive impairment (MCI) or earlier – molecular amyloid imaging shows remarkable promise in this. Both structural and functional imaging have clear positive predictive utility. Serial imaging may have added value.

3. Safety markers – therapies aiming to disrupt the pathological process may well carry a number of risks for cerebral damage – MRI is now being included as a safety assessment in a number of trials.

4. Measurement of disease-progression – this is perhaps the most important and yet controversial area with claims being made for the value or otherwise of several imaging modalities.

The Alzheimer's disease neuroimaging initiative is the largest systematic study to try and address these issues with head-to-head comparisons. Ultimately the process of finding safe therapies that will slow this devastating disease is likely to require close collaboration between industries and academia and will need to harness the best technologies in imaging and other biomarkers.

Alzheimer's Disease (AD): target population and development of biological markers for early detection and characterization. Harald Hampel, Chair of Psychiatry, Trinity College Dublin, Ireland Alzheimer Memorial Centre, University of Munich, Germany

The pathophysiologic process leading to neurodegeneration in AD is thought to begin long before clinical symptoms develop. Existing therapeutics for AD improve symptoms, but increasing efforts are being directed toward the development of therapies to impede the pathologic progression of the disease. Although these medications must ultimately demonstrate efficacy in slowing clinical decline, there is a critical need for biomarkers that will aid early pre-symptomatic, preclinical and clinical detection and patient characterisation, stratify pre-clinical and clinical patient populations for trials, indicate whether a candidate disease-modifying therapeutic agent is actually altering the underlying degenerative process.

The clinical syndrome of dementia and the criteria for its severity are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR of the APA and in ICD-10 (F00-F03) of the WHO. For the effective and consistent evaluation of patients a stable diagnostic framework must be followed. After a rigorous exclusion of other diagnosable causes of dementia the establishment of a clinical AD subtype diagnosis can be further specified by using the NINCDS-ADRDA criteria. Knowledge of AD is rapidly advancing, thus the diagnostic criteria currently used may need revision and updating. Whereas sensitivity has been shown very good to excellent, specificity has been much lower. Currently patients with probable AD according to the NINCDS-ADRDA criteria are the most appropriate group in whom to study the effects of drugs. Revised criteria are being discussed in the APA DSM-V and WHO ICD-11 working groups. In particular, the potential implementation of additional operationalised neurobiological criteria (using both neurochemical and imaging information) to the classical descriptive clinical criteria within the diagnostic process may aid to an earlier and more accurate characterisation of AD patients.

A number of in vivo neurochemistry and neuroimaging techniques, which can reliably assess aspects of physiology, pathology, chemistry, and neuroanatomy, hold promise as biomarkers. These neurobiological measures appear to relate closely to pathophysiological, neuropathological and clinical data, such as hyperphosphorylation of tau and tangle formation, the amyloidogenic pathway, rate of atrophy and cognitive decline, as well as risk of future decline. As this work has considerably matured, it has become clear that biological measures may serve a variety of potential roles in early

clinical and pre-clinical diagnosis, clinical trials of candidate therapeutic agents for AD, depending in part on the question of interest and phase of drug development.

The status of current core feasible neurochemical biomarker research was summarized and potential applications of these markers outlined for future clinical practise and studies, particularly with respect to early detection and prediction, patient stratification and characterisation, i.e. the predefinition of a homogeneous patient population at risk ("enriched population"), which may allow better evaluation of therapeutic efficacy in distinct trial populations.

Overlap between vascular dementia (VaD) and dementia of the Alzheimer's type (AD): an epidemiological perspective (Miia Kivipelto Aging Research Centre, Karolinska Institutet, Stockholm, Sweden)

Based on Scandinavian population studies (CAIDE and Kungsholmen Project), there is evidence for a significant overlapping in terms of risk factors, clinical features and pathology especially among elderly persons between vascular dementia and dementia of the Alzheimer's type. `Pure´ AD and ´pure´ VaD can be considered the opposite ends of a dementia aetiology *continuum*, where most cases are ´in between´. Cerebrovascular changes including silent brain infarcts and white matter lesions detected with brain imaging are associated with an increased risk of not only VaD but also AD. Epidemiological studies have reported an association between midlife high blood pressure, serum cholesterol levels, obesity and subsequent dementia. Also diabetes, even borderline diabetes, and metabolic syndrome have been related with VaD and AD. Recent results from the CAIDE (cardiovascular risk factors, aging and dementia) study also link several lifestyle related factors including saturated fat intake, physical inactivity, alcohol consumption and smoking to dementia risk, especially among ApoE4 carriers. AD and VaD share several vascular and lifestyle factors, which supports the importance of vascular mechanisms in the development of dementia and integrated interventional strategies.

Vascular dementia (VaD) or dementia with cerebro-vascular disease? Changes in concepts. Jean-Marc Orgogozo INSERM U-897 University of Bordeaux, France

VaD is an etiological category of dementia in ICD-10- This includes dementia resulting from cerebral ischemia or haemorrhage (post-stroke dementia). Rarer is the dementia from global hypoperfusion (post-CABG or post-CHF). In the current definition of dementia excessive emphasis is put on memory disturbances, based on the cortico-hippocampic type (dementia of the Alzheimer's type) and is not applicable to the sub-cortical and frontotemporal types, more frequents in VaD. Actually the DSM-IV definition is loose: memory loss plus cognitive impairment equates dementia if (and only if) there is a functional loss. Executive dysfunction is often prominent in VaD: should this symptom be alternative to memory loss as first criterion? In facts executive dysfunction drives the early functional loss in these patients. Notably according to WHO ICD-10 dementia is not only a dysmnesia.

Diagnosis of VaD according to NINDS-AIREN criteria implies a diagnosis of dementia plus a diagnosis of cerebrovascular disease with history of cerebro-vascular disease (CVD) (over the last 3 months), neurological examination and neuroimaging. Probable/Possible diagnosis of VaD can be made on the basis of temporal relationship between CVD and dementia, abrupt onset/stepwise progression and absence of disorders that could account for deficits (e.g. AD). However alternative definitions may be considered; *VaD:* cognitive impairment causing dementia, both resulting from ischemic or hemorrhagic CVD (post-stroke dementia); or from hypoperfusion (hypotension, post coronary artery bypass graft [CABG] or post congestive heart failure [CHF]). *Vascular cognitive disorder (VCD):* a diagnostic category that includes any degree of cognitive impairment resulting from cerebro-vascular disease [CVD]. *Vascular cognitive impairment (VCI):* corresponding to isolated cognitive dysfunction, not qualifying as dementia.

Executive (Control) Functions (ECF) was added to the DSM-IV definition of dementia in 1994. "Command and control" of complex goal directed action like initiation, sequencing and monitoring of complex behaviour. Executive dysfunction is expressed as disorganized thought, behaviour, or emotions. ECF is a characteristic feature of VaD although not mandatory in current criteria; it includes

difficulties in planning, organization, problem-solving, conceptualization, and mental flexibility. ECF leads to difficulties in performing instrumental activities of daily living (IADL) such as managing finances, phoning, transportation, medication, engaging in hobbies.

Key clinical features differentiate **Alzheimer's dementia** (insidious onset, progressively deteriorating course; no early focal neurological signs and no vascular damage on brain imaging) from **vascular dementia (**sudden onset, fluctuating, stepwise course with plateaus; early focal neurological symptoms/signs and evidence of relevant vascular brain damage).

VaD and vascular cognitive impairment may become the most common cause of cognitive loss and behavioural changes in the elderly, particularly in the older-old, causing a major public health problem.

Lewy body dementias (Ian McKeith, Institute for Ageing and Health, Newcastle University, UK).

Lewy body dementias can be divided into two clinical syndromes, both of which are related to similar neuropathological and neurochemical abnormalities which include alpha-synuclein aggregates (Lewy bodies and Lewy neurites), beta-amyloid deposition, and dopaminergic and cholinergic deficits.

Parkinson's disease dementia (PDD) describes the occurrence of dementia in a patient with a previous history of motor PD. Dementia with Lewy bodies (DLB) is a *de novo* dementia presentation in which motor parkinsonism may emerge (in up to 75% of cases) at a later stage. The two clinical syndromes overlap and an arbitrary "1 year rule" is used to distinguish them with at least one year of PD before dementia being required to diagnose PDD. Operationalised clinical criteria have been agreed internationally for the clinical diagnosis of both syndromes and those for DLB have been autopsy validated to have high specificity. Sensitivity can be increased by use of a "possible DLB" category augmented by neuroimaging biomarkers.

Lewy body dementias are the second most common cause of neurodegenerative dementia and are associated with high levels of functional disability, costs of care and impaired quality of life. They present multiple treatment targets including fluctuating cognitive impairment, psychiatric and behavioural disturbances with recurrent visual hallucinations; motor parkinsonism, sleep disorders and autonomic dysfunction including cardiovascular instability, falls, early urinary and faecal incontinence and sexual dysfunction.

The general principles underlying trial design for Alzheimer's disease (AD) are applicable to DLB and PDD i.e. symptomatic treatment, disease modification and primary prevention. Cognitive, functional and global outcome measures are appropriate assessments of putative treatments but instruments designed for AD may need adaptation to take account of the particular cognitive profile of DLB and PDD and the multiplicity of impairments contributing to patient disability. Placebo controlled studies of cholinesterase inhibitors have already been conducted in DLB and PDD and a marketing license granted for the latter indication. Examples of trials exist in which DLB and PDD have been enrolled as separate populations or alternatively as a single pooled sample. Evidence to date indicates that the Lewy body dementias are a treatment responsive group.

The Lewy body dementias DLB and PDD are relatively common disorders; internationally agreed diagnostic criteria exist for both and the goals of treatment are similar to those for AD although there are more to be taken into consideration. Outcome measures exist for most clinical domains but differ slightly from AD and may require some adaptation. Treatment effects in DLB and PDD are likely to be similar however two distinct trial populations may be considered. Demonstrating differences in treatment response between DLB and PDD subjects would generally require very large samples.

Frontotemporal Dementias: more than an exclusion diagnosis? Alessandro Padovani, Department of Neurological Sciences, University of Brescia, Italy

Frontotemporal Dementia (FTD) prevalence in the adulthood is still debated. It is characterized by the heterogeneous onset of cognitive deficits in language and executive functions, along with personality changes and behavioural dysfunctions. Motor impairments including parkinsonism or motor neuron

disease are variably represented. FTD progresses to severe dementia more rapidly as compared to AD. It encompasses different clinical and biological entities, namely the behavioural variant FTD (bvFTD), the Semantic Dementia (SD), and the Progressive Non-Fluent Aphasia (PNFA). Recently, Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration Syndrome (CBDS) have been considered under the same label of frontotemporal lobar degeneration (FTLD) by some authors, because their clinically and neuropathologically overlapping.

FTLD is a sporadic disease, but familial forms with an autosomal dominant trait of inheritance have been identified, accounting for 30-50% of cases. These findings have clearly highlighted a crucial role of genetic background in FTLD, most likely greater than in other forms of neurodegenerative dementias.

In the last couple of years, the improved understanding of genetic determinants of FTLD has allowed to differentiate these disorders either on the basis of clinical symptoms or on the basis of neuropathological abnormalities. Autopsy studies recognized Tau- positive and Tau-negative FTD, the latter also known as FTD with ubiquitin inclusions. It has also been demonstrated that the first are linked to mutations within MAPT gene, whilst the second to mutations within progranulin gene.

Several efforts have been made to distinguish these two neuropathological entities, and it has been reported that progranulin mutations lead to language deficits as clinical hallmark. Ongoing studies are trying to better describe the relationship between neuropathology and clinical features, and future operationalised criteria should be developed.

FTD is associated with high levels of functional disability, costs of care and impaired quality of life.

Nowadays, no approved pharmacological treatments are available yet for FTD. In an era of treatment that targets disease-mechanism, it would be desirable that clinical assessment should be developed to discriminate molecular/genetic determinants of FTLD pathology. Pharmacological trials, which also take into account clinical features, biological and neuroimaging characteristics, are mandatory. Treatments targeting the pathogenetic key-players in FTD are warranted.

Conclusions

The CHMP Efficacy Working Party, the Scientific Advisory Group for CNS and the EMEA Scientific Secretariat organised this workshop with a panel of European Experts actively involved in the clinical and epidemiological research in dementia. The FDA/CDER contributed to the debate clarifying the current regulatory views for development of new medicines for dementia in the USA.

All the participants, Academia, Patients, Healthcare Professionals, Industry and Regulators were able to convey their respective views during each session and particularly during the debate session in the afternoon. The outcomes of discussions during this workshop will be taken into consideration for the finalisation of *Dementia of the Alzheimer's type and other dementias;* and for *Parkinson's disease* EMEA guidance documents currently under revision.

Apologies

Russell Katz (CDER/FDA) joined from Washington *via* teleconference. Eric Abadie, Barbara van-Zwieten, Tomas Salmonson, Catherine Deguines, Jean-Pierre Lépine and Serge Bakchine were unable to join the meeting due to adverse weather conditions.

Disclaimer

The elements originating during the discussion do not constitute a formal specific advice on a particular product or class of products. The positions expressed by the Experts or the CHMP/EWP, SAG-CNS or the EMEA Scientific Secretariat during that Meeting will not be regarded as binding in relationship to any aspect of subsequent institutional work.

Presentations

Introductory Remarks & Scope — **C. Sampaio**

This includes the debate on the updated guidelines on AD and PD

Alzheimer's Dementia (AD) — **K. Broich, M. Rossor**

1. **Target Population** — **H. Hampel**

This includes biomarker approach to AD early detection and characterisation.

2. **Primary End-Points** — **K. Broich**

This focuses on the main requirements for AD new medicines.

3. **Update on issues relating to the use of neuroimaging in trials in AD** — **N. Fox**

Available data on neuroimaging techniques as a follow-up tool (including **ADNI**, PIB-PET, etc)

Vascular Dementia (VD) — **M. Donaghy**

1. **Target Population** — **M. Kivipelto**

This focuses on the epidemiologic approach to dementias

2. **Specific End-Points** — **JM. Orgogozo**

This focuses on the operational approach to vascular dementia

Questions

Parkinson's and Frontotemporal dementias — **C Sampaio, I. McKeith**

3. **Target Population and specific End-Points** — **I. McKeith**

State-of-the-art of diagnostic criteria and opening for therapeutic needs (specific-or-not) for PD dementias

4. **FTD: more than an exclusion diagnosis?** — **A. Padovani**

Canada and US groups recently drew attention to this challenging sub-group of dementias with little memory impairment and difficult-to-manage behavioural burden. A model for an integrated clinical /molecular approach?

Questions

AFTERNOON SESSION:

Focus on development of new medicines for Dementia	**K. Broich**
1. The challenge of new developments for dementias : the FDA point of view Questions	**R. Katz**
2. Guidelines on dementias : the challenge of disease-modifiers development Questions	**C. Sampaio**
3. Received Comments to the published guidelines As a synthetic review	**S. Del Signore**
4. General discussion with the Stakeholders *This will allow the participants to bring up their views in terms of innovative approaches (use of) and CT implementation (feasibility)*	**K. Broich**
5. Concluding Remarks and Future Actions	**S. Del Signore**