What are we trying to prevent in Alzheimer disease?

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Within aging societies, the number of individuals suffering from Alzheimer disease (AD) is consistently increasing. This is paralleled by intense research aimed at improving treatment options and potentially even fostering effective prevention. The discussion on relevant outcomes of such interventions is ongoing. Here, different types of currently applied outcomes in the treatment of AD at the dementia stage, but also at the pre-dementia stages of mild cognitive impairment (MCI) and asymptomatic preclinical AD are discussed. Regulatory agencies require effects on the clinical measures of cognition and function. In novel disease-modifying therapy trials, biological markers are used as secondary and exploratory outcomes. Additional outcomes of great relevance for the individual patients are neuropsychiatric symptoms, quality of life, and goal attainment. In addition, costs and cost-benefit ratios are of interest for the reimbursement of interventions.

Keywords: Alzheimer disease; clinical trial; dementia; disease modification; mild cognitive impairment; outcome; preclinical Alzheimer disease; symptomatic treatment

Background

Alzheimer disease (AD) is the most common cause of dementia. According to current concepts, AD refers to a pathological brain process, which extends over several years to decades. Core pathologic features are aggregation of the amyloid-β (Aβ)-peptide, which originates from the amyloid-precursor protein (APP) and aggregation of the neuronal protein tau. These processes are accompanied by synaptic dysfunction, inflammatory reactions, neurodegeneration, and related molecular mechanisms. The accumulation of pathology evolves over many years within the preclinical phase, during which the individual does not experience any symptoms or functional effects of this process. Subsequently, symptoms develop slowly over many years. Longitudinal studies suggest that around 10 years before the stage of dementia, subtle cognitive decline begins, which is often accompanied by the subjective experience of cognitive worsening. This stage may also be accompanied by mild behavioral symptoms such as depression, anxiety, apathy, and sleep disturbances. Once the dysfunction in cognition becomes apparent and detectable on neuropsychological testing, the stage of mild cognitive impairment (MCI) is reached. MCI is defined by objective cognitive dysfunction with still fully intact functioning and independence in daily living. After the MCI stage, which may also last for a number of years, dementia gradually develops. Demencia is defined by substantial impairment in cognitive capacities, which causes functional disabilities (e.g., severe memory impairment, orientation deficits, language comprehension problems, apraxia) with the requirement for support in everyday life. The dementia stage can be divided into a mild, a moderate, and a severe stage. The latter is characterized by full dependency on care and the inability to perform basic activities of
daily life. This is often accompanied by severe language impairment, full loss of memory, and motor symptoms. Behavioral neuropsychiatric symptoms often occur, sometimes at a severe degree. Such symptoms include, but are not limited to, delusions, hallucinations, agitation, severe apathy, depression, anxiety, and severe sleep disturbances.7 Care demands usually increase, with the progression of cognitive and functional decline reaching the maximum at the severe dementia stage. The late stage is also associated with higher costs and with frequent institutionalization. Caregiver’s burden and health risks are significant throughout the dementia stage of AD. Death occurs after a limited number of years within the dementia stage of AD.8

Neuropathologic changes are progressive and extended brain tissue loss with a particular focus on medioc-temporal regions and cortical areas occur in the late stage of the disease. Based on this disease course, different aims of treatment and prevention have been developed over the past decades.

**Treatment goals of symptomatic therapy**

In the late 1980s and early 1990s, the currently licensed drugs for symptomatic treatment of either mild-to-moderate (acetylcholinesterase inhibitors) or moderate-to-severe (memantine) Alzheimer dementia were developed.9 Since then, the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) have required the proof of efficacy on two parallel end points, namely global cognition (both) and global clinical change (FDA) or activities of daily living (EMA) for such symptomatic treatment at the different dementia stages. In the trials for regulatory approval of such drugs, proof of AD pathology in the individual patient is usually not required. The label is formulated based on the clinical syndrome of dementia.

The gold standard for testing cognition in the symptomatic treatment of Alzheimer dementia is the Alzheimer’s Disease Assessment Scale, cognitive part (ADAS-Cog) of which different versions are available.10 Within the ADAS-Cog, different domains of cognition are tested in a paper-pencil approach. A total score is calculated. For cognition at the advanced dementia stage, the Severe Impairment Battery (SIB) is available.11 Global clinical change, which is the additional FDA requirement, is assessed with physician-based rating scales. The second end point, which is required by the EMA, refers to the ability in performing activities of daily living (ADL). A number of different ADL scales are in use in clinical trials.12 For both, clinical change and ADL capacities ratings, information provided by the caregivers is incorporated.

All currently licensed drugs for the treatment of Alzheimer dementia showed superiority against placebo on both of these end points in at least two independent 6-month trials. The effect size of the drugs on the respective outcomes are small to moderate and range between a Cohen’s of 0.3-0.5,13,14 Clinical trials show that on average a slight improvement in performance is observed for a period of 3 to 6 months. After that, further decline occurs. If these drugs are stopped even at the stage of progressive worsening, decline is accelerated.15 Thus, many guidelines propose to continue such drugs long-term, beyond the 6-month period, which is the basis for licensing. Novel symptomatic treatments are currently tested as an add-on to the licensed medication using the same end points and trial durations.

There have been extensive debates on whether effects on cognition per se are relevant patient-related outcomes and whether the effect size of such drugs is sufficient to provide and adequate benefit-risk ratio.16 At present nearly all international guidelines on the treatment of Alzheimer dementia have concluded that these drugs are of benefit and are recommended for treatment. The clinical benefit is supported by the effect on the clinical change and ADL scales, which reflect outcomes related to daily functioning.

**Symptomatic outcomes for the pre-dementia state of Alzheimer disease**

With the development of novel drugs, which aim at slowing disease progression, and with the failure of such drugs in clinical trials in mild to moderate dementia, research has moved the field of pre-dementia disease
detection and intervention. The target population for most current trials is patients with MCI and combined groups of MCI and mild dementia, in whom cerebrospinal fluid (CSF) biomarkers or positron emission tomography (PET) indicate the presence of amyloid pathology.\textsuperscript{17}

In such target populations, cognitive performance is the main outcome. The ADAS-Cog is optimized for the mild to moderate dementia stage. Therefore, additional, more demanding cognitive test batteries have been generated mainly from observational cohort studies in these patients groups. One of these cognitive test sets is referred to as the neuropsychological test battery (NTB).\textsuperscript{18} At present, there is not yet a specific cognitive test battery, which could be considered the gold standard in the MCI/mild dementia population. Until now, there have been no drug trials which showed an effect on these cognitive scales as a primary outcome. This may be due to the lack of efficacy of the respective compounds, but may also be at least partly caused by insufficient sensitivity for change of the current instruments.

Patients at the MCI/mild dementia stage only show minor or no impairment of ADL scales, which are used in mild-to-moderate Alzheimer dementia clinical trials. Scales for the assessment of complex instrumental ADL are under development and provide evidence for subtle impairment in functioning already in this patient group.\textsuperscript{19} To date, however, such scales are not used as primary end points in clinical trials.

Due to the subtlety of effects in this patient group on standard scales for Alzheimer dementia clinical trials, the FDA and the EMA have recently agreed upon accepting a single primary end point in MCI/mild dementia clinical trials, which usually have a duration of 12 to 24 months. The currently proposed single primary end point for such trials is the Clinical Dementia Rating Scale (CDR).\textsuperscript{20} This instrument rates cognitive and functional capacities based on a physician interview with the patient and the caregiver. Besides a global score, which can be used for classification of patients into different stages of the cognitive impairment, it also provides a continuous measure (CDR sum of boxes, CDR-SOB). The CDR-SOB is considered to reflect a clinically meaningful combined assessment of cognition and function. Up to now, however, studies in the respective target population have failed to demonstrate an effect on the CDR-SOB as a primary end point. Once first compounds achieve this goal, the effect size will guide the discussion on clinical relevance.

Measuring cognitive change at the pre-mild cognitive impairment stage of Alzheimer disease

A few clinical trials aim at impacting on the disease course and on cognition even in the pre-MCI stage of AD. Examples of such studies are the A4 trial in amyloid positive cognitively normal individuals\textsuperscript{21} as well as the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU)\textsuperscript{22} and the Autosomal Dominant Alzheimer’s Disease (ADAD)\textsuperscript{23} Trial, which perform studies in cognitively normal individual with causal monogenic mutations. In these long-term studies, which may exceed a number of years, sensitive cognitive batteries, also derived from observational cohorts, are employed to detect subtle change in cognitive performance over time as the primary end point. One example of such instruments is the Preclinical Alzheimer Cognitive Composite (PACC).\textsuperscript{24} At present all of these studies are ongoing and results are to be expected within the next few years.

Alzheimer disease biology as an outcome of treatment

The leading concept of recent drug development in AD is disease modification. This refers to impacting on the core molecular pathology of the disease plus achieving a slowing of symptom progression.\textsuperscript{25} The main current molecular target is the deposition of amyloid. Several trials in different patient populations have been performed or are ongoing. Molecular effects are measured by biomarkers. In phase 2 and 3 clinical trials, such biomarker outcomes are measured as secondary or exploratory end points in addition to the cognitive and functional primary outcomes.

Anti-amyloid approaches are capable of reducing cerebral amyloid load and A\textsubscript{β} production. Amyloid plaque reduction by monoclonal antibodies against amyloid has been demonstrated with PET.\textsuperscript{26} Postmortem analysis of individuals who received active immunization against amyloid showed a correlation between the antibody titer and the reduction of amyloid plaque load.\textsuperscript{27} The
| INSTRUMENT/O UTCO ME                              | CONTENT/USE/COMMENTS                                                                 |
|--------------------------------------------------|--------------------------------------------------------------------------------------|
| **Cognitive tests**                              |                                                                                      |
| Alzheimer Disease Assessment Scale, cognitive part (ADAS-Cog) | Global cognition, required by EMA and FDA in mild-to-moderate AD trials, different versions available |
| Severe impairment battery (SIB)                  | Global cognition in moderate-to-severe dementia                                        |
| Neuropsychological test battery (NTB)            | Global cognition and individual cognitive domains, optimized for mild cognitive impairment (MCI) |
| Preclinical Alzheimer cognitive composite (PACC)  | Global cognition and individual cognitive domains, optimized for preclinical Alzheimer disease |
| **Clinical ratings**                             |                                                                                      |
| Clinical dementia rating scale (CDR)             | Rating of cognition and function in different domains, often single primary end point in MCI/mild AD trials |
| Clinician’s interview-based impression of change with caregiver input (CIBIC-plus) | Rating of the overall status of the patient in comparison to an earlier time point |
| Alzheimer’s Disease Cooperative Study/ activities of daily living scale (ADCS/ADL) | Assessment of functional capacities in activities of daily life (ADL), all dementia stages, distinction between instrumental and basic ADL, several other ADL scales available |
| **Behavioral symptom assessments**               |                                                                                      |
| Neuropsychiatric inventory (NPI)                 | Quantitative rating of twelve different behavioral domains, caregivers’ burden rating included, short version available |
| Cornell scale for depression in dementia (CSDD)  | Measures symptoms of depression                                                       |
| Cohen-Mansfield agitation inventory (CMAI)       | Measures agitation and aggression in dementia                                          |
| Dementia care mapping (DCM)                      | Observation-based assessment of mood and well-being in severe dementia                |
| **Additional outcomes**                          |                                                                                      |
| Quality of life in Alzheimer’s disease scale (QoL-AD) | Assesses different aspects of quality of life in dementia, other scales available      |
| Goal attainment scale (GAS)                      | Develops individual goals of an intervention in a hierarchical fashion                |
| Resource utilization in dementia (RUD)           | Measures the quantity of used health care resources in a defined timeframe            |
| Institutionalization                             | Time to nursing home placement                                                       |
| **Biological markers**                           |                                                                                      |
| Amyloid                                          | Aggregated amyloid can be measured with positron emission tomography (PET), Aβ42 can be quantified in the cerebrospinal fluid (CSF) |
| Tau, phosphorylated tau (ptau)                   | Both can be quantified in the CSF, Tau indicates neuronal injury, ptau indicates AD-related modification of Tau |
| Neurofilament light (NFL)                        | Can be measured in the CSF and in the blood, corresponds to neurodegeneration         |
| Hippocampal volume, whole brain volume           | Can be measured with magnetic resonance imaging                                       |

*Table 1. Examples of different types of outcomes in clinical trials in Alzheimer disease.*
inhibition of the β-secretase with respective inhibitors leads to a significant reduction in Aβ42 reduction in the brain. Therefore, it is possible to impact on specific molecular mechanisms related to AD and to measure such effects. At present however successful lowering of cerebral amyloid has not been associated with a slowing of symptom progression, which is an unexpected outcome of the majority of recent trials. In one small study with the monoclonal antibody Aducanumab, however, reduction of amyloid as detected with PET was accompanied by a dose dependent slowing of disease progression as measured with the CDR-SOB as an exploratory outcome over 12 months in mild Alzheimer dementia. This promising compound is currently being tested in two phase 3 international clinical trials.

There is a growing number of clinical trials with anti-tau compounds. At present, however, data is too limited to understand the effects of anti-compounds on biomarker of total tau, phosphorylated tau (pTau) or tau-PET as well as on clinical outcomes.

An unspecific marker of neurodegeneration, which also occurs as a core feature in AD, is the volume reduction of brain tissue as detected with magnetic resonance imaging (MRI). In trials with active and passive anti-amyloid immunization, the hippocampus and other measures of brain volume, such as whole brain volume and ventricular size, were used as indicators of the impact of amyloid-lowering on neurodegeneration. To general surprise, the volume reduction of the hippocampus was accelerated within the verum groups in comparison with the placebo groups in a number of trials. This finding, however, was not accompanied by accelerated cognitive decline. The cause of accelerated brain volume loss in anti-amyloid treatment is not resolved at present.

Trials with other compounds, which potentially stimulate neuroplasticity to a certain extent, provide opposite results. In a placebo-controlled trial with donepezil, a slowing of volume reduction of the hippocampus in prodromal AD as the primary outcome was observed. This was, however, not associated with cognitive effects. In a placebo-controlled trial with the medical food Fortasyn Connect, slowing of hippocampal volume reduction was also observed as a secondary end point in a 12-month trial. This effect was paralleled by a slowing of decline on the CDR-SOB. The primary cognitive end point of that study, however, was negative. Overall, established biomarkers, which are used to identify AD pathology, have provided evidence for molecular target engagement of novel compounds. The relationship with symptoms and thus, the potential usefulness of a surrogate marker of treatment effects in AD is unclear.

Novel biomarkers are under development. As an example, Neurofilament Light Chain (NFL) has been identified as a marker of axonal injury and neurodegeneration in CSF and plasma. In multiple sclerosis, there is promising evidence that NFL may serve as a meaningful marker of disease-modifying treatment. Trials in AD are ongoing. Overall, the need for biomarkers, which serve beyond diagnostics and extend to treatment monitoring and outcome prediction is substantial.

Additional outcomes related to patient benefit

From the very beginning of cognitive decline up to severe dementia, patients experience neuropsychiatric symptoms (NPS), which include, but are not limited to depression, anxiety, apathy, agitation, hallucinations, delusions, and sleep disorders. In the majority of current clinical trials effects of drugs or interventions on these symptoms are measured as secondary end points. The most commonly used instrument is the Neuropsychiatric Inventory (NPI), which cover all NPS domains quantitatively and also assesses the associated caregivers’ burden. Currently licensed drugs for the treatment of mild, moderate, and severe Alzheimer dementia have shown modest positive effects on such symptoms on a global level. There is no clear evidence yet that such symptoms are affected by novel disease-modifying approaches.

There are many studies which apply specific drugs from psychopharmacology, such as antipsychotics and antidepressants to improve single NPS (e.g., depression, psychosis, agitation). Often specific scales exist for such individual symptoms, such as the Cornell Scale for Depression in Dementia (CSDD) or the Cohen-Mansfield Agitation Inventory (CMAI). Overall, some antipsychotics show benefits on specific target symptoms. At the same time, these drugs are associated with increased mortality rates and other side effects in
dementia. Thus, the use should be limited to cases with very clear indication and the treatment duration should be as short as possible. Antidepressants have a more favorable side effect profile. However, their efficacy in reducing symptoms of depression seems to be lower than in patients with depression, but without dementia. Greater improvement of NPS than with medication is achieved by nonpharmacological interventions, in particular by those, which focus on communication and environment. A number of instruments are available to measure quality of life (QoL) in patients with dementia. One main challenge in assessing QoL in dementia is cognitive impairment, particularly in the domains of memory and language, which interferes with the report on QoL as a highly subjective construct by the patient him- or herself. In particular, if symptoms of anxiety and depression occur inconsistently, the overall report by the patient at a given time point may be of insufficient validity. Due to the subjective nature of QoL, study partners or caregivers cannot easily serve as substitutes. One approach of assessing QoL in dementia indirectly, is by constant observation as developed in nursing science via Dementia Care Mapping (DCM). In DCM, patients with severe dementia are observed over a long period of time and their emotional expressions are constantly recorded. Based on such very extended assessment it is possible to estimate the patient’s wellbeing and to guide and modify interventions.

A highly patient-centered outcome is the goal attainment approach. Here, individual goals related to a specific intervention are defined within a clinical interview with the patient and the caregiver. These goals are ranked in order of importance. At follow-up visits, it is discussed with the patient and the caregiver, if steps towards this goal were achieved or not. The meaningfulness of this outcome is significant, as it is individually tailored. The Goal Attainment Scale (GAS) has been used in randomized controlled clinical trials in Alzheimer dementia. However, challenges with regard to standardization of the method and the interpretation of data have to be acknowledged.

Cost-related outcomes

Due to the extensive costs generated by AD, particularly at the late disease stages, there is a high interest in the potential of cost reduction by individual interventions. The Resources Utilization in Dementia (RUD) instrument is most commonly used in clinical trials. It measures all costs related to care over the previous weeks. As yet, however, efficacy of interventions on the RUD has not yet been solidly shown.

Another frequently assessed outcome is institutionalization, referring to transition from the home environment to a nursing home. Since institutionalization is associated with increased cost, it can be considered a health economic outcome. In prospective randomized clinical trials, institutionalization is not a common outcome, because in mild dementia or pre-dementia stages, at which most trials are performed, it is a rare event. Institutionalization was assessed in the DOMINO trial (donepezil and memantine in moderate to severe AD) in the United Kingdom (UK), which tested the impact of randomized withdrawal of the acetylcholinesterase inhibitor donepezil after long-term treatment in patients with moderate to severe dementia, who showed cognitive decline. The study found a significantly lower rate of institutionalization within the first 6 months in those who were randomized to treatment continuation in comparison with those who were discontinued.

It has to be acknowledged that institutionalization and other measures of cost are very much dependent on the health care system of the respective countries and regions. Thus, conclusions on cost savings of interventions cannot easily be transferred between health care systems.

Conclusion

Alzheimer disease is a very complex condition with very many facets and many potential goals of intervention. The majority of drugs currently under development are focusing on disease modification by targeting key molecular mechanisms of the disease such as amyloid deposition and tau aggregation. Biomarkers provided evidence of target engagement of such compounds. So far, however, none of these novel compounds has shown a robust effect on the clinical symptomatology of the patients. In the current absence of effective prevention of dementia, it is crucial to further develop pharmacological and nonpharmacological interventions, which aim at improving and stabilizing symptoms at all disease stages, such as cognition and ADL function, but also neu-
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ropropsychiatric symptoms and quality of life of patients and caregivers. Once novel drugs have shown efficacy, effect sizes, patient-related benefit, and cost-benefit evaluations will guide the discussion on reimbursement and ultimately decide on access to such innovations for the patients. In the end, we will hopefully achieve successful early treatment development with pharmacological and lifestyle-based interventions, which will significantly delay disease progression and will keep patients independent for prolonged periods of time.

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