ABSTRACT: This new section to the guidelines was added due to the recognition that clinical milestones are useful indices of the progression of dementia in patients with Alzheimer’s disease and could help in the development of stage-specific targeted therapy. This review specifically looks at clinical milestones that could be used in clinical trials, such as global function, function, behaviour, caregiver burden, and quality of life milestones. It also addresses the possible use of biological and surrogate markers for use as milestones - which may eventually replace clinical milestones. It concludes that current definitions of dementia must be broadened beyond cognition alone to include some of the domains listed.

RÉSUMÉ: Stadification et étapes importantes de la maladie. Cette nouvelle section a été ajoutée aux lignes directrices parce qu’on reconnaît que les étapes cliniques sont des indices utiles de la progression de la démence chez les patients atteints de la maladie d’Alzheimer et peuvent aider à développer un traitement approprié à chaque étape de la maladie. Cette revue examine les étapes cliniques qui pourraient être utilisées dans les essais cliniques comme la fonction globale, la fonction, le comportement, le fardeau pour les soignants et les étapes de la qualité de vie, de même que la possibilité d’utiliser des marqueurs biologiques et des marqueurs de substitution comme critères d’étapes qui pourraient éventuellement remplacer les étapes cliniques. En conclusion, les définitions actuelles de la démence doivent être élargies au-delà de la cognition seule afin d’inclure certains autres domaines.

Furthermore, to select an appropriate milestone, one must consider many factors like the stage of the disease and the observable outcome being measured. For example, if cognition was chosen, it would be important to consider how cognitive symptoms progress over the course of the disease. When used alone as a criterion for clinical trials, cognition is inadequate when screening a person with AD at any stage. In the mild stages of AD, there is little cognitive loss, some functional loss of instrumental Activities of Daily Living (ADL), but not self-care ADL, and relatively few emergent neuropsychiatric symptoms. In contrast, moderate AD is characterized by more rapid cognitive decline, reduction in capacity to perform instrumental ADL and self-care ADL, as well as new neuropsychiatric symptoms. In moderate AD, longitudinal rates of cognitive and functional decline have been measured using the Mini Mental State Examination (MMSE), the Alzheimer disease assessment scale-cognitive (ADAS-cog), and the Disability Assessment for Dementia scale with annual decline of 2.3, 11.4, and 15.1 points, respectively. The ADAS-cog score in moderate AD is also positively correlated with annual rate of cognitive decline on the MMSE and an increased risk of reaching clinical milestones. The MMSE and ADAS-cog, however, are sensitive enough for measuring cognitive loss in the severe stages of AD, and the measurement of cognition in severe AD requires other scales, such as the Severe Impairment Battery. Interestingly, the decline on the Disability Assessment for Dementia scale can still be observed even over a period as short as six months and changes in behaviour can also be detected with the neuropsychiatric inventory (NPI).

Recent trials have evaluated changes in global functioning using a version of the Clinician's Interview-based Impression of Change (CIBIC), behavioural changes with the Neuropsychiatric Inventory (NPI), and the Zarit Burden Interview (ZBI) for caregiver burden. Diagnostic research criteria have been published by the American Psychiatric Association and others utilizing longitudinal studies examining annual changes in clinical milestones. These include progression of cognition, function, rates of nursing home placement, and death. These clinical milestones of disease progression in AD have been validated using a multidimensional assessment of cognition, behavioural, and function with the Clinical Dementia Rating Scale (CDR) and the Global Deterioration Scale (GDS). High-risk milestones, with cumulative frequencies exceeding 50% at three years, include change on the CDR rating, loss of IADLs, failure to recall three words on the MMSE, and decline of the total MMSE score to below 10. Loss of dressing and toileting activities occur at intermediate rates, while loss of eating ability is rare. The GDS has been used to chart the longitudinal course of normal aging and dementia with respect to mortality, institutionalization, and clinical changes. Patients with GDS greater than or equal to 4 are more likely to show negative outcomes, specifically, institutionalization with stage 4, 5, or 6 associated with an increased mortality in comparison with aged control populations.

In contrast with cognition and global function, data with high predictive power are relatively scarce with respect to other clinical milestones, such as conversion from normal to mild cognitive impairment (MCI) to dementia; the emergence, course, and persistence of neuropsychiatric symptoms; and measures of quality of life for both patients and caregivers. Healthy, community-dwelling old-old who experience cognitive decline over a decade (CDR=0.5 or MMSE score <24) do not universally progress to dementia. Cognitive and functional decline tend to be linear over time and are, therefore, easier to measure; whereas caregiver burden peaks and decreases in parallel to the neuropsychiatric symptoms which show great individual variation with much less predictability.

For example, the spectrum of neuropsychiatric disturbances have been tracked by following AD patients over eight years; however, their emergence and course is not as predictable, making it more challenging to use them as clinical milestones and for disease staging in clinical trials. Patients often, but inconsistently, show symptoms of anxiety and depression in early-stage dementia, while other more severe neuropsychiatric manifestations emerge in the moderate stages, only to abate in the later stages when motor signs and incontinence become prominent.

The first example of a behaviour in dementia is depression. Depression is one of the most frequent psychiatric complications of AD, affecting as many as 50% of patients. Symptoms, however, do not persist with less than half the original patients having persistent symptoms at 1 year. The presence of depressive symptoms does not appear to affect the course of cognitive impairment at 12 months; but, remission of depressive symptoms in AD at 12 months leads to a decreased frequency of other non-cognitive disorders and to a slight improvement in the assessment of global function. A past psychiatric history of depression and the number of depressive symptoms at baseline is a risk factor for the emergence and persistence of depressive symptoms at 12 months with a higher likelihood of needing longer duration of treatment. Clinical trials for depression in AD would need to consider incorporating non-cognitive and global measures in addition to those measuring the reduction in depressive symptoms.

Another example of a neuropsychiatric symptom in dementia is agitation. An increase in generalized motor activity (“agitation”) is common and persistent in early AD, but is very difficult to define operationally and challenges clinicians and researchers alike. Aggressive behaviours are most prevalent in people with more severe dementia and are easier to characterize than agitation make aggression suitable targets for study in late stage dementia. Verbal aggression is the most common and longest-lasting form of aggressive behaviour, but aggressive resistance and physical aggression are the most likely to persist until death. No correlation exists between aggressive behaviour and age, gender, or time since onset of dementia.

Finally, there is the example of hallucinations, the presence of which is selectively associated with more rapid cognitive decline in AD, and may be useful as a clinical marker in late dementia trial designs. Caregiver burden (CB) and quality of life (QOL) are also potentially useful as milestones. They are both complex processes, influenced by diverse patient and caregiver characteristics and are more challenging to use as clinical milestones in trial design.

Patient functional and neuropsychiatric impairments are major factors to increase CB, which, in turn, is a significant predictor for the death or institutionalization of the patient. Day
treatment programs, home care services, and caregiver education are significant protective factors which reduce premature institutionalization.17

Three key QOL milestones are confinement to home, lack of activity, and lack of positive affect, as reported by patient proxies. Time-to-onset of all three is predicted by disease severity and is sensitive to disease progression. Patients whose dementia worsens over follow-up are more likely to reach each milestone and may be useful for studying treatment in advanced AD.28

Finally, cost of care may also be a useful surrogate marker in trial design, as it is strongly correlated with disease progression. Cost is factored into longevity, community-based and nursing home care,29 and increases dramatically with increasing disease severity.30 Institutionalization is the largest component of cost, accounting for as much as 84% of the cost for people with severe disease. For subjects living in the community, unpaid caregiver time and use of community services are the greatest components of cost and increase with disease severity.31

PART B

BIOLOGICAL AND SURROGATE MARKERS

Biological and surrogate markers are important tools in studying AD as their use may reduce sample sizes in clinical trials and serve as more direct proof of disease modification.

A number of reliable, noninvasive neuroimaging techniques are correlated with rates of cognitive decline and the risk of future decline, making them excellent candidates for use as biomarkers. Of these, hippocampal atrophy is perhaps the best studied structural MRI marker of AD. In fact, serial volumetric measures of the hippocampus may be useful as an early marker to identify individuals with AD decades before initial clinical expression.32 Patients with MCI have marked atrophy of the hippocampus and amygdala compared with healthy elderly MRI scanning. Antemortem MRI scans and autopsy findings predict decline at early and preclinical stages.33 Furthermore, atrophy of the hippocampus and amygdala on MRI in cognitively intact elderly people predicts dementia diagnosis during a six-year follow-up.34 Hippocampal and amygdala volumes are strongly associated with the risk of dementia; the age-, sex-, and education-adjusted hazard ratio per 1-SD decrease in volume is 3.0 (95% confidence interval, 2.0-4.6) for the hippocampus and 2.1 (95% confidence interval, 1.5-2.9) for the amygdala.

Other early markers may include the Braak-histopathological staging system associated with grades of clinical symptomatology and total intracranial volume (ICV) in the smallest quartile known to significantly increase the risk of cognitive impairment (either MCI or dementia).35,36 The hazard ratios associated with atrophy are similar in persons without memory complaints or low cognitive function at baseline. Compared with those remaining free of dementia, baseline brain volumes are 17% smaller in persons who receive a clinical diagnosis of dementia within two to three years after MRI and 5% smaller in those whose conditions are diagnosed six years after MRI. Postmortem MRI scanning shows that hippocampal volume is strongly correlated with Braak neurofibrillary stage.37

The sensitivity of hippocampal volume is 100% and the specificity ranges between 83% and 100%. Combinations of hippocampal volume with other measures may be a reliable index of AD neuropathology, especially at more advanced Braak stages.38

Tracers to directly visualize and measure AD neuropathology are being actively investigated using various neuroimaging techniques.39 The tracers can be safely administered to humans to label proteins associated with the fibrillar β amyloid. The visualization of these direct biomarkers of neuropathology should greatly aid diagnostic and monitoring of patient treatment, and validation of these techniques as surrogate markers is expected to enhance translational research between animal models and humans. Examples of these techniques include: 1) In vivo PET-based detection of β amyloid with increased retention of Pittsburgh compound-B found in frontal and tempo-parietal regions in patients with clinical AD;40 2) FDG-PET scans of patients with probable AD demonstrate prominent temporoparietal hypometabolism compared to controls; 3) fMRI shows decreased medial temporal lobe activation during performance of memory tasks in mild AD patients compared with non-demented older individuals.41 Refinement in the quantitative metrics, specificity, and more clear utility in prodromal or presymptomatic AD states is still needed, however.

Inflammatory and oxidative damage come closest to meeting criteria proposed for useful biomarkers for diagnosis of AD. Both result in biochemical changes in blood and cerebrospinal fluid. Reduced CSF levels of the 42 amino acid form of Abeta (Abeta42) and increased CSF levels of total tau (T-tau) and hyperphosphorylated tau (p-tau), have been found in numerous studies. These markers make it easier to identify incipient AD in MCI, differentiate between AD and several important differential diagnoses, including normal aging, depression, alcohol dementia, and Parkinson’s disease, and also to identify Creutzfeldt-Jakob disease in cases with rapidly progressive dementia. These biomarkers have with high sensitivity but low specificity with respect to other dementias. The addition of phospho-tau (P-tau) seems to increase the specificity, since normal levels are found in other dementias and in cerebrovascular disease.42

Novel ways to conceptualize AD may also add exciting new opportunities to look for biomarkers. For example, the notion of re-classifying AD as a vascular disorder may lead to development of new biomarkers and subsequent discovery of a useful treatment.43,44 Studies of vascular cognitive impairment (VCI) incorporates interactions between vascular etiologies, changes in the brain (infarcts, white matter lesions, atrophy), host factors (age, education), and cognition, with a causal connection between stroke or Cerebrovascular disease (CVD) and AD.45 In addition, studies of chronic brain hypoperfusion linked to AD risk factors may allow preclinical detection and pharmacotherapeutic action of symptoms.46,47

CONCLUSION

In conclusion, the concept of disease staging and clinical milestones for AD must consider and incorporate multiple domains including cognition, function and behaviour. Inclusion of patient and caregiver quality of life, caregiver burden, and cost factors as outcome measures would give trials much greater clinical and pharmacoeconomic impact. These broader and more
comprehensive, but still proxy, markers of the disease would be gradually correlated to the biological underpinnings of AD. Biological and surrogate markers, such as noninvasive imaging as well as blood and CSF measures, become easier to study, more objective, reliable, specific and sensitive. It is anticipated that this would lead to faster, less costly studies with fewer patients. It would also help to track disease progression and modification, thereby eventually replacing clinical milestones and staging as primary outcomes in clinical trial design.

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