The future of alzheimer disease immunotherapies in Saudi Arabia: Consensus statement of the Saudi Chapter of Cognitive and Behavioral Neurology

Haythum O. Tayeb, MBBS, MSc FRCP(C), Roaa A. Khallaf, MBBS, Taim A. Muayqil, MBBS, MSc, Walid A. Alkeridy, MBBS FRCP(C), Fawwaz S. Alibrahim, MBBS, FRCP(C), Omar A. Alfaify, MBBS, Najeeb Qadi, MD, Frank I. Tarazi, MD, PhD.

ABSTRACT

مرض الزهايمر مشكلة صحية عالمية كبرى. العلاجات الدوائية القياسية الحالية للمرض لا تفضي إلا إلى تحسن إدراكي وسلوكي بسيط ومؤقت ولا تغير مسار المرض. في عام 2021 صرحت هيئة الغذاء والدواء الأمريكية استثنائيا باستخدام دواء أديوكينوماب – وهو جسم مضاد لبروتين أميلويد – في علاج الزهايمر كأول علاج محتمل أنه يغير مسار المرض. للأسف، نظرا لعدم وضوح فعالية العلاج ولآثاره الجانبية قامت الجهات الصحية في معظم أنحاء العالم بتقييد استخدامه. ثم صرحت هيئة الغذاء والدواء الأمريكية باستخدام دواء آخر من مضادات للأميلويد وهو دواء ليكانيماب. كما أن دواء دونانيماب في المراحل الأخيرة من التجارب السريرية. في هذه الورقة العلمية، قامت الشعبة السعودية لطب أعصاب الإدراك والسلوك الأعصاب الإدراكي والسلوكي بصياغة بيان إجماعي يتضمن استعراضا لتطورات العلاجات المناعية لمرض الزهايمر وما تعنيه للمرضى ومقدمي الرعاية الصحية والنظام الصحي في السعودية. في هذا البيان تسرد الشعبة التوصيات فيما يتعلق بوصف علاجي أديوكانوماب وغيره من العلاجات المناعية المستقبلية لمرضى الزهايمر السعوديين، وتصف الموارد والبنى التحتية والأبحاث اللازم تحقيقها لتحويل رحلة المريض والمسارات السريرية لزهايمر في السعودية إلى ما يمكن تقديم العلاجات المناعية لمرض الزهايمر في المملكة في المستقبل.

Alzheimer Disease (AD) constitutes a major global healthcare problem. Standard AD pharmacotherapies offer only modest transient cognitive and behavioral benefits. Aducanumab, an amyloid monoclonal antibody, was the first disease modifying agent to be approved for AD treatment. However, concerns about its efficacy and side effects led regulatory institutions around the world to restrict its use. Lecanemab was the second amyloid antibody to receive accelerated approval for use in early AD. This review and consensus statement was prepared by the Saudi Chapter of Cognitive and Behavioral Neurology to review the current developments in AD immunotherapies from a Saudi perspective. We outline recommendations with regards to offering aducanumab and other future immunotherapies to Saudi AD patients. We describe resources, infrastructure, research, and clinical practice changes that must be attained to transform the patient journey and clinical pathways of AD in Saudi Arabia to enable offering AD immunotherapies in Saudi Arabia.

Neurosciences 2023; Vol. 28 (2): 77-84
doi: 10.17712/nsj.2023.2.20220133

From The Neuroscience Research Unit and the Mind and Brain Studies Initiative (Tayeb), Division of Neurology, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, from the Department of neurology (Khallaf), Neuroscience Center, King Fahad Specialist Hospital Dammam, from Neurology Unit (Muayqil), from the the Department of Medicine (Alkeridy), College of Medicine, King Saud University, Riyadh, from the Neurology Division (Alibrahim), Department of Medicine, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, from the Department of Neurology (Alfaify), Prince Sultan Military Medical City, from the Neuroscience Centre (Qadi), King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, and from the Department of Psychiatry and Neuroscience (Tarazi), Harvard Medical School and McLean Hospital, Belmont, USA

Received 17th November 2022. Accepted 3rd January 2023.

Address correspondence and reprint request to: Dr. Haythum O.Tayeb, The Neuroscience Research Unit and the Mind and Brain Studies Initiative, Division of Neurology, Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia. E-mail: hostayeb@kau.edu.sa
ORCID ID: https://orcid.org/0000-0002-9453-8463

Alzheimer disease (AD) is the most prevalent neurodegenerative disorder in the world. It is estimated that more than 50 million individuals around the world suffer from AD and this number is expected to reach 75 million by 2030.[1] In Saudi Arabia, there is a lack of population-based epidemiological studies but the overall prevalence of AD is expected to be in agreement with the global data. It is estimated the overall prevalence of AD in Saudi Arabia is 5%, with a progressive increase in prevalence after the age of 65 years.[2–4] In the Middle East, it is estimated that the prevalence of dementia is 10% in individuals aged 75-79 years, 16% in individuals aged 80-84 years, and 29% in individuals

who are 85 years and older.[1] The AD causes incurable and debilitating progressive memory impairment and cognitive decline. This is invariably associated with progressive disability, eventually resulting in complete dependency, behavioral dysregulation, vulnerability to infections and other complications, and death.[1,5] The socioeconomic burden of AD on societies is huge. The global cost of dementia care is estimated to be more than US $800 billion dollars in 2015,[1] and is expected to reach US $1.6 trillion dollars by 2050.[6] The pharmacotherapeutic options to treat AD are limited to acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine and the NMDA receptor antagonist, memantine. Although these medications confer temporary mild cognitive and behavioral benefits in AD, they do not alter AD's progression and clinical outcomes.[7] Decades of basic science and clinical research have failed to find an effective disease modifying agent that prevents or delays the progression of AD.[7] Without such an agent, there is a huge unmet healthcare need and unaddressed public health problem.[1]

In June of 2021, the US Food and Drug Administration (FDA) granted a conditional approval for aducanumab, a monoclonal antibody targeting amyloid species thought to contribute to the pathophysiology of AD.[8] The decision was unique in terms the FDA unprecedently used the "accelerated approval program" to approve a new therapy for a neurological disorder. Aducanumab became the first medication to be approved for AD in 18 years since the approval of memantine and had the potential promise of being the first approved AD modifying agent. The approval of this medication, however, was a controversial decision.[9] Although statistically significant clinical benefit was demonstrated in a pivotal phase III clinical trials (EMERGE), another pivotal clinical trial (ENGAGE) failed to meet its primary and secondary endpoints.[8] The FDA's conditional approval required the pharmaceutical company Biogen to conduct a confirmatory phase 4 trial to verify the anticipated clinical benefits of the drug, with the potential for withdrawing the aducanumab from the market if the clinical benefits were not confirmed.[8]

The FDA's accelerated conditional approval of aducanumab initiated a global debate whether this treatment should be offered to patients with AD. Several leading academic medical centers in the US declined to offer aduncanumab for their AD patients. The US Center for Medicare and Medicaid Services (CMS) announced it would cover the costs of treatment with aducanumab only if patients were enrolled in clinical trials under their "Coverage with Evidence Development" program, which is a major restriction to who will have access to the treatment.[10] Relevant regulatory and insurance agencies in Europe and Japan restricted or refused authorization to use aducanumab in treating AD patients.[11] On the other hand, the United Arab Emirates (UAE) approved treatment with aducanumab based on the FDA's approval, becoming the second country after the USA to approve the drug and allowing prescribers to offer this treatment to all patients with AD.[12] More recently, the US FDA granted a similar accelerated approval to lecanemab, another monoclonal amyloid antibody.[13]

It is important to ponder what these developments mean for AD patients, their families and healthcare providers in Saudi Arabia and the Gulf region. How does the available evidence about aducanumab apply in Saudi Arabia and the Gulf region? Should patients consider treatment with this agent? Should clinicians recommend it for their patients? The proximity of the UAE may be enticing for many able patients and families dealing with AD to cross the border and get treated with aducanumab. What should guide the positions of professional societies and regulatory agencies dealing with aducanumab, lecanemab, and with potential future immunotherapies?

Answers to these questions require a careful review of the evidence with the Saudi context kept in perspective, and necessitate expert consensus that chart the path forward toward offering current and future immunotherapies to AD patients in Saudi Arabia. This paper constitutes a consensus statement of the Saudi Chapter of Cognitive and Behavioral Neurology (SCBN), a chapter of the Saudi Neurology Society. We review the state of the evidence behind amyloid immunotherapies in AD that have reached late-stage clinical trials, with a focus on perspectives and implications relevant for Saudi Arabia and the Gulf region. We then state reasons for and against use of aducanumab in Saudi AD patients, as well as recommendations with regards to resources and infrastructural transformations that must be fulfilled to be able to offer immunotherapies to AD patients in an ideal setting.

The amyloid cascade hypothesis. More than a hundred years ago, Alois Alzheimer described the histopathological hallmarks of AD, including extracellular brain deposits of aggregated amyloid β, termed the amyloid plaques, and intraneuronal deposits

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Table 1 - Reasons for and against offering aducanumab and lecanemab to Saudi patients at this stage.

For	Against
Statistically significant cognitive and behavioral benefits were demonstrated in the EMERGE clinical trial	The clinical significance of benefits demonstrated in the EMERGE trial is questionable
Subgroup analysis of data collected from thr ENGAGE clinical trial showed cognitive benefits of a sufficient duration exposure to 10 mg/kg of aducanumab	No statistically significant cognitive and behavioral benefits demonstrated in the ENGAGE trial
Clarity-AD trial demonstrates benefit in AD patients	Lecanemab is only supported with one trial with other trial results pending
Effective, dose-dependent clearance of cerebral amyloid as determined by amyloid PET scance	Clearance of cerebral amyloid has not been confirmed as a biomarker that correlated with clinical efficacy
There is a huge unmet need to develop disease-modifying therapies for patients with AD and decrease the family and socioeconomic burdens of the disease	There is a risk of doing harm and even increasing the risk of mortality associated with some forms of ARIA. Careful monitoring of AD patients throughout treatment is essential to detect early signs of ARIA
Approving AD immunotherapies takes a long time; these are the first new for AD in nearly 2 decades	Approval of new, potentially better, immunotherapies may be impending, eligibility for which may be complicated if patients were already treated with aducanumab
	Lack of representation of patients with different genetic and ethnic backgrounds in clinical trials
	Saudi-specific gaps in the patient care journey, including lack of streamlined clinical care pathways, definitively validated neuropsychological and behavioral assessment tools, availability of CSF and PET scan biomarkers

Table 2 - Consensus recommendations regarding clinical practice and resource requirements for developing AD immunotherapy programs in Saudi Arabia.

Clinical practice recommendations
- A multidisciplinary cognitive and behavioral neurology clinic setting is required for AD immunotherapy programs.
- Supervision by neurologists, geriatricians and/or psychiatrists with subspecialty training in behavioral neurology is required.
- Offering treatment only to amnestic MCI or early AD patients who otherwise meet criteria for being good candidates for treatment, excluding patients with moderate and severe patients with AD, and patients with other forms of dementia or history or cerebrovascular events.
- Adherence to protocols of pivotal clinical trial of each of the immunotherapeutic agents being used, particularly with regards to inclusion criteria, dosing, neuropsychological and biomarker assessment, and frequent safety monitoring to detect and minimize the risks of ARIA.
- Collection of phase 4 data for medications not sufficiently demonstrated to be effective and safe in Saudi AD patients by extrapolation of data from phase III clinical trials
Resources and infrastructure
- Recruitment and training of neurologists, geriatricians, and/or geriatric psychiatrists in cognitive and behavioral neurology or dementia
- Recruitment and training of neuropsychologists, psychotherapists and key supportive staff to work in dementia clinics
- Validating the minimum neuropsychological and behavioral psychometric tools: ADAS-Cog 13, MMSE, CDR, NPI, MCI-ADCS, others.
- Regular and immediate access to MRI scans
- Access to reliable amyloid tests: amyloid PET scans and amyloid tracers
- Access to reliable and widely available testing of CSF a-beta42 and p-tau, apoE4 genetic testing

of tau, termed the neurofibrillary tangles (NFTs). Today's most prevalent theory to explain AD, termed the "amyloid cascade hypothesis", stipulates a major role for amyloid in the pathogenesis of AD. It is thought that amyloid β, due to several genetic and acquired reasons, accumulates progressively in the brains of patients who would ultimately develop AD. Amyloid deposition is believed to start decades before patients become symptomatic. This amyloidopathy would initiate a cascade of neuronal injury and synaptic dysfunction, leading to formation of NFTs and neuronal cell death. This leads to progressive dysfunction of neuronal networks subservient of memory and other cognitive, executive, and behavioral functions, thereby leading to the progressive symptoms of the disease. The fact that autosomal dominant genetic forms of AD involve mutations in genes related to amyloid metabolism supports a central role for amyloid in the pathogenesis of AD. These genes include presenilin 1, presenilin 2, and the amyloid precursor protein.[7]

Although the amyloid cascade hypothesis remains the longest surviving and prevalently considered theory to explain the pathophysiology of AD, doubts about its validity and alternative contending theories have long existed. Not all patients with amyloid plaques develop symptomatic AD, and many patients with AD symptomatology have no abnormal accumulation of toxic amyloid plaques. As discussed below, numerous

clinical trials of anti-amyloid agents failed in improving the behavioral symptoms of AD despite their ability in reducing the cerebral amyloid burden. On the other hand, the topographic distribution and deposition of tau closely follows brain networks that subserve memory. Tau deposition has been demonstrated in several other neurodegenerative disorders. This has raised the possibility that tauopathy rather than amyloidopathy may be central to AD pathology, and that amyloidopathy may be an epiphenomenon rather than a causative force in AD pathogenesis. Alternative theories have established themselves as key pathogenic mechanisms in AD, including neuroinflammation, neurovascular dysfunction, insulin resistance, immune system abnormalities and glial cell dysfunction. These are now the focus of extensive preclinical and clinical investigation and may lead to new and improved approaches in AD treatment.[7]

Amyloid directed therapies in AD. A large gamut of amyloid directed therapies have been examined in preclinical studies and clinical trials enrolling AD patients to see whether altering the amyloid cascade would modify the relentlessly progressive cognitive and functional decline seen in AD.[7] Drug trials aiming to reduce amyloid production failed for different reasons at various stages in clinical trials, shifting emphasis to drugs that would instead clear deposited cerebral amyloid. Active immunization with antigens derived from the amyloid β protein was demonstrated to clear cerebral amyloid effectively in clinical trials of AD patients but failed to improve cognitive and behavioral symptoms. Moreover, it was associated with unacceptable complications, including aseptic meningitis.[7] Accordingly, trials shifted to passive immunization with monoclonal amyloid antibodies. These trials focused on patients with early AD and mild cognitive impairment (MCI) due to AD, assuming that prior immunotherapy trials failed in part due to focus on moderate and late AD patients who could potentially have reached a stage of irreversible neurodegeneration.[7] The most notable monoclonal antibodies that were tried in the early 2000s included bapinuzumab and solanezumab.[13] These were two monoclonal antibodies targeting different epitopes in the β amyloid protein. Despite initial promise, both these agents failed to significantly delay the progression of AD.[14] The search for an effective amyloid antibody continued, however, which brings us to the first approved monoclonal antibody for AD: aducanumab.[9]

Aducanumab clinical trials. Aducanumab is a monoclonal antibody targeting amyloid β oligomers and fibrils. After passing phase I and II studies, two phase III trials were conducted to test its efficacy and safety in AD patients. The EMERGE and ENGAGE trials were large, multicenter, double-blind, placebo-controlled, phase III trials of monthly intravenous infusion of aducanumab in patients with early AD and MCI due to AD.[8,15] These two trials recruited 3285 patients between 50-85 years of age with MCI and early AD (MMSE=24-30) who had positive amyloid positron emission tomography (PET) scans. These patients were randomized to receive either placebo, low-dose aducanumab (3 or 6 mg/kg after titration), or high-dose aducanumab (6 or 10 mg/kg after titration). The planned treatment duration was 78 weeks. The primary endpoint of the studies was the change in the Clinical Dementia Rating Scale Sum of Boxes (CRD-SB). Secondary endpoints included scores on the Mini-mental Status Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13), and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale adapted for Mild Cognitive Impairment (ADCS-ADL-MCI). A tertiary end point was score on the Neuropsychiatric Inventory (NPI). In addition, the effect of aducanumab treatment on amyloid load was assessed using [18F]-florbetapir positron emission tomography (PET) scans and CSF β amyloid 1-42 CSF levels.[8,15]

Results from both ENGAGE and EMERGE trials demonstrated that aducanumab was effective in significantly and dose-dependently reducing the cerebral amyloid burden as demonstrated by amyloid PET and CSF studies. ENGAGE and EMERGE differed however in terms of reaching the clinical endpoints. ENGAGE failed in demonstrating significant differences in any of the clinical endpoints between the placebo and treatment groups. The EMERGE succeeded in demonstrating that patients receiving the high-dose of aducanumab worsened significantly less than the low-dose treatment and placebo groups, with a CDR-SB benefit of -0.39 points (95% CI=-0.69 to -0.09), a -1.4 benefit on ADAS-Cog 13 (95% CI= -2.46 to -0.34), and a benefit of 1.7 points on the ADCS-ADL-MCI scores. These results were robust and statistically significant, although their clinical significance has been questionable.[8,15] Subsequent analyses of data from ENGAGE demonstrated that its negative results could have been related to the fact that the proportion of patients that was titrated rapidly enough to reach the target 10 mg/kg was lower than hoped for, resulting in an insufficient duration of exposure to that dose. Specific subgroup analysis of data of ENGAGE patients who stayed on the high dose for a sufficient duration had similar responses to those seen in EMERGE.[8]

The most significant adverse event of aducanumab is the occurrence of Amyloid Related Imaging

Abnormalities (ARIA). This is a phenomenon that is seen with most amyloid removing agents and is thought to result from an inflammatory reaction to the removal of amyloid. The ARIA includes ARIA-E (where the brain MRI reveals vasogenic edema), ARIA-H (where there are microhemorrhages in addition to vasogenic edema), and ARIA-H with superficial siderosis. ARIA can be mild, moderate, or severe depending on how sizable the edematous areas are and the number of microhemorrhages and superficial siderosis. The incidence of ARIA in patients receiving the 10 mg/kg dose of aducanumab in EMERGE and ENGAGE was 41.3%. ARIA-E occurred in 35.2%, whereas ARIA-H in 19.1%, and ARIA-H with superficial siderosis in 14.7%. Only a quarter of patients with ARIA were symptomatic with headache, confusion, or nausea. In addition, most ARIA cases resolved in 3-4 months. Mild ARIA is typically managed conservatively without interruption of treatment, whereas moderate ARIA necessitates delaying or even terminating treatment. In 10% of the cases, ARIA was severe and necessitated discontinuation of the treatment. A single death was potentially attributable to ARIA-H.[15,16] Nonetheless, there is a need to monitor patients treated with aducanumab by sequential MRIs every 3-6 months to detect early signs of ARIAs and intervene if needed to ameliorate their adverse events.

Following the announcement of ENGAGE and EMERGE results, the US FDA granted a controversial approval to use aducanumab in AD patients. This approval was conditional upon a requirement that Biogen conduct a phase 4 trial, collecting real world data about the clinical effects of aducanumab. Currently, Biogen and Eisai are conducting this trial, known as the ICARE AD-US study.[15]

Future Alzheimer immunotherapies in the pipeline. Several other monoclonal antibodies are in advanced stages of clinical trials. Donanemab (Eli Lilly) gantenerumab (Roche), and Lecanemab (Biogen/Eisai). have all been demonstrated by amyloid PET scans to significantly reduce the amyloid burden in patients with AD. They have shown promising results in phase II trials, and have progressed in phase III clinical trials.[17,18] that recruited large numbers of patients with amyloid-PET-positive early AD. The ongoing trial of donanemab, TRAILBLAZER-ALZ 2, has interestingly been designed so that patients are stratified according to their tau PET burden, hoping to compare the clinical response of patients with cerebral amyloidopathy according to whether they have an intermediate or high associated tau burden.[19,20] Results of donanemab trials are expected in the near future. Gantenerumab has the advantage of being a subcutaneous injection over the other AD immunotherapies that are available only in intravenous formulations. However, the recent results of the Phase III GRADUATE I and II trials were disappointing as both trials failed to meet their primary endpoints of slowing clinical decline in people with early AD. Roche attributed the failure of trials to the lower-than-expected clearance of amyloid by gantenerumab.[21]

Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, was demonstrated to confer significant cognitive benefit in early AD in the CLARITY-AD trial. This phase III trial showed that early AD patients treated with lecanemab had a a lower mean increase in the CDR-SB at 18 months in comparison to placebo (1.21 vs 1.66,; $p<0.001$).[13] There were also significant benefits in secondary endpoints, including the ADASCog 14 (difference: −1.44; $p<0.001$); the Alzheimer's Disease Composite Score (ADCOMS; difference: −0.050; $p<0.001$) and ADCS-ADL-MCI (difference: 2.0; $p<0.001$).[13] These findings led the US FDA to grant an accelerated approval for use in early AD. Of note, the drug carries a similar risk for ARIA to aducanumab and at least 1 deaths has been suspected to be related to cerebral hemorrhage associated with the drug.[13]

Discussion. The AD is a significant health challenge facing the Saudi society. News about the approval of aducanumab sparked hope in the minds of many patients, families and healthcare professionals facing the daily challenges of AD in Saudi Arabia and worldwide. The question is whether aducanumab treatment should be offered to patients with AD in Saudi Arabia. After all, this was the first therapy approved for treatment of AD in nearly two decades. It appeared to fill the desperate unmet needs of AD patients and their families. There are reasons for and against offering aducanumab as a new therapy for AD patients in Saudi Arabia (**Table 1**). There is ample reason for caution. Evidently, the positive results of EMERGE and the cognitive benefits demonstrated in the subset of ENGAGE patients exposed long enough to the highest dose of aducanumab suggest that aducanumab may be ready for use in clinical practice to treat AD patients.[8] However, it cannot be overlooked that one of the 2 pivotal phase III trials was negative and failed to meet primary or secondary endpoints. In addition, the positivity of the EMERGE trial was argued to potentially relate to a poorer than usual trajectory for the placebo group in EMERGE in comparison with the placebo group in ENGAGE.[8,5] Moreover, the clinical meaningfulness of the cognitive benefit demonstrated in the trials is questionable. It has been estimated that a clinically meaningful change in

the CDR-SB is 1-2 points, which is clearly higher than the 0.39 demonstrated in the EMERGE trial.[22] The American Academy of Neurology (AAN) Guidelines Subcommittee report highlighted that aducanumab's benefits are of questionable clinical meaningfulness.[5] This is especially important in the context of the potential approval of other immunotherapies, which are in late stages of clinical development. Starting patients on aducanumab may potentially complicate their eligibility for these newer potentially improved immunotherapies and may require careful switching to avoid an increased risk of ARIA and other undesirable adverse events.

In Saudi Arabia, there are specific reasons warranting caution with regards to widely approving and using aducanumab. The cohorts recruited for the pivotal trials EMERGE and ENGAGE do not represent the typical Saudi AD patients. Patients in these trials were mostly white Caucasians, with very few patients from minority groups. One cannot therefore extrapolate from the data of these trials to judge the efficacy and effectiveness of aducanumab in patients with AD in Saudi Arabia who are of different ethnic and genetic backgrounds. In addition, most patients recruited in EMERGE and ENGAGE had 14-18 years of education. A significant proportion of Saudi AD patients are illiterate or of lower education than those recruited in the trials.[4] This may mean that they have lower levels of cognitive reserve and a lower amyloid burden to cognitive burden ratio,[23] which may impact treatment responsiveness. Furthermore, illiteracy complicates cognitive assessment, particularly without an assessment tool validated for assessing illiterate Saudi AD patients and staging their disease based on cognitive performance.[24]

The more recent approval of lecanemab sparked yet another hope for AD patients and families. However, it must be kept in mind that the lecanemab data are very comparable to the aducanumab data, with similarly questionable benefits, similar rates of ARIA, and similar draw backs related to the study population. Furthermore, lecanemab is only backed by one phase III trial and additional longer term data are needed.[13,21]

In addition, to be able to offer immunotherapy to Saudi AD patients, there are obstacles at various steps of the journey of AD medical care in the Saudi context. The journey of AD patients starts with early accurate diagnosis. To date, none of the key assessment tools used in pivotal immunotherapy trials was definitively validated for the purpose of diagnosing, staging, treating, and following Saudi AD patients. This has practical significance. For example, it has been suggested based on the psychometric properties of the MMSE that patients with a score of 21/30 are candidates for immunotherapy. This eligibility cut off may be different in the AD population in Saudi Arabia.[25] Initial key work has been published documenting use in Saudi individuals of the MMSE, the Montreal Cognitive Assessment (MoCA), the Bristol activity of daily living scale, and the NPI in Saudi individuals.[25–28] The Arabic version of the battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was validated in older Omanis.[29] Some additional tools, including the CDR and the ADAS-Cog, were validated in other Arab countries.[30,31] Additional studies must build on this work to examine the need for cultural modifications, demonstrate clinical practicality, as well as validity and reliability of cut off scores of the various assessment tools in Saudi patients who may be candidates for immunotherapy.

Another diagnostic obstacle that must be bypassed to enable accurate diagnosis and staging of AD and determine eligibility for immunotherapy programs is the lack of easily available and reliable AD biomarker testing. methods to measure amyloid biomarkers prior to the initiation of treatment. Measuring CSF aβ 42 and the aβ 40:42 ratio is available but not widely used. Furthermore, patients in the pivotal immunotherapy trials were recruited based on amyloid PET scan results and not CSF analysis. Although CSF analysis may indicate the presence of toxic amyloid species, it is not certain that it reflects cerebral amyloid plaque burden, which is the main source of amyloid PET scan positivity.[32] Therefore, offering AD immunotherapies to patients based on CSF results only may not be sufficiently adherent to the criteria of phase III trials. This is in addition to the issue of patient and family reluctance to have lumbar puncture to obtain CSF samples. Blood based amyloid biomarkers are in development and hold great promise,[33] but they are still not sensitive enough and it is also not clear they would reflect amyloid PET scan burden. Therefore, to use a reliable intervention to accurately assess the amyloid burden prior to initiation of treatment with aducanumab, amyloid PET scans remain the best diagnostic tool to rely on. Having said that, amyloid PET scan tracers are not currently available in Saudi Arabia yet. It has been suggested, however, that a clinical diagnosis of probable AD, made by experienced and trained clinicians using appropriate diagnostic criteria may be sufficient to presume the presence of AD pathology with or without support of biomarkers.[32] However, the authors recommend remaining adherent to recruitment using amyloid PET scan and considering a move to other means of judging the presence of amyloidopathy later on when prescribers in AD immunotherapy programs develop experience and enough data are collected to demonstrate validity

of other means of measuring the amyloid burden.

Finally, another challenge in Saudi Arabia is that the infrastructure to support dementia care is currently fragmented. AD patients mostly receive care in non-specialized clinics without access to resources or a standardized behavioral neurology or memory clinic setups that would enable accurate diagnosis, treatment and follow up of AD patients. This may have been manageable with the previous repertoire of treatment options but would likely be insufficient for developing sophisticated AD immunotherapy treatment programs. **Table 2** describes the authors' recommendations regarding minimal requirements for developing optimal immunotherapy programs for AD patients in Saudi Arabia. The journey of patients with dementia starts with early case finding and referral to the appropriate dementia care program, accurate comprehensive diagnostic testing, longitudinal monitoring, and finally support and management. To ensure successful delivery of the novel disease modifying therapy in the near future, it is crucial to build the required capacity that fulfills these best practices for appropriate dementia care management, including the actual administration of novel therapies. It is crucial to transform care to streamlined, multidisciplinary clinics that involve subspecialty trained behavioral neurologists, geriatricians, psychiatrists, neuropsychologists, psychotherapists, and supportive services is crucial to be able to offer the specialized services to AD patients. This would require a strategic plan to assess resources required for this transformation, including the need to train physicians, psychologists, therapists, and other supportive staff. While planning these strategic transformations, the cost effectiveness of aducanumab and other immunotherapies may become a concern. It has been demonstrated that even if the original cost of aducanumab treatment in the US was halved to $28,000/year, it would still not be cost-effective.[34] This raises a question of resource allocation in a country that is overhauling its healthcare system. It may be an overall disservice to the community of AD patients and their families to divert resources away from projects that may directly impact their current quality of life or from future research or infrastructure projects to fund a medication that is not supported by a solid evidence base. Finally, The issues encountered in Saudi Arabia may not be unique to the Saudi setting and likely apply at a global level.[35] The emerging treatments will require urgent development of a global framework and close collaboration with all stakeholders including the patients, specialists, the pharmaceutical industry, regulators and payors to collectively address these issues.[36]

Conclusions. This is a momentous time in the history of AD. The approval of the first two disease-modifying therapies opened the door to other potentially beneficial amyloid monoclonal antibodies to continue their clinical development and march with more confidence towards FDA approval. The personal and socioeconomic burdens of AD are huge, and these medications may indeed be what patients and families living through the long journey of this horrible disease are waiting for. However, we still do not have sufficient evidence to unequivocally recommend immediate use of any of these immunotherapies yet. In addition, there are major infrastructural changes and specific practice obstacles that need to be overcome in the context of Saudi Arabia, the Gulf countries and the Arab world at large to make these therapies more accessible. The pivotal clinical trials did not recruit patients that represent the typical Saudi AD patients. We recommend waiting for additional clinical studies before deciding to offer any of the AD immunotherapies to patients in Saudi Arabia. AD care in Saudi Arabia must transition to streamlined multidisciplinary clinics staffed by subspecialty trained physicians, neuropsychologists and supporting staff that are able to accurately diagnose, stage and treat AD. Key clinical assessment tools need to be validated in Arabic. Amyloid PET scans need to be made available and accessible to patients prior to initiation of treatment. Before all these recommendations are accomplished, offering immunotherapies to AD patients in Saudi Arabia may be premature.

Acknowledgment. *We are grateful to the Saudi Neurology Society for supporting the Saudi Chapter of Cognitive and Behavioral Neurology and for supporting this work.*

References

1. Nichols E, Szoeke CE, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. ***Lancet Neurol*** 2019; 18: 88-106.
2. El-Metwally A, Toivola P, Al-Rashidi M, Nooruddin S, Jawed M, AlKanhal R, et al. Epidemiology of Alzheimer's Disease and Dementia in Arab Countries: A Systematic Review. ***Behav Neurol*** 2019; 2019: e3935943.
3. Albugami M, Qadi N, Almugbel F, Mohammed A, Alttas A, Elamin A, et al. The Demographic Characteristics and the Risk Factors of Dementia in SAUDI Elderly. ***Am J Psychiatry Neurosci*** 2018; 6: 1-8.
4. Alsebayel FM, Alangari AM, Almubarak FH, Alhamwy R. Prevalence of Dementia and Its Associated Risk Factors Among Geriatric Patients Visiting Primary Healthcare Centers in Riyadh, Saudi Arabia: A Cross-Sectional Study. ***Cureus*** 2022; 14: e24394.

5. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. ***Alzheimers Dement*** 2022; 18: 700-789.
6. Velandia PP, Miller-Petrie MK, Chen C, Chakrabarti S, Chapin A, Hay S, et al. Global and regional spending on dementia care from 2000-2019 and expected future health spending scenarios from 2020-2050: An economic modelling exercise. ***EClinicalMedicine*** 2022; 45: 101337.
7. Tayeb HO, Yang HD, Price BH, Tarazi FI. Pharmacotherapies for Alzheimer's disease: beyond cholinesterase inhibitors. ***Pharmacol Ther*** 2012; 134: 8-25.
8. Biogen. Combined FDA and Applicant PCNS Dru sgs Advisory Committee Briefing Document. Published November 6, 2020. Accessed October 16, 2022. https://www.fda.gov/media/143502/download
9. Tagliavini F, Tiraboschi P, Federico A. Alzheimer's disease: the controversial approval of Aducanumab. ***Neurol Sci*** 2021; 42: 3069-3070.
10. DiStefano MJ, Alexander GC, Polsky D, Anderson GF. Public opinion regarding US Food and Drug Administration approval of aducanumab and potential policy responses: A nationally representative survey. ***J Am Geriatr Soc*** 2022; 70: 1685-1694.
11. Lythgoe MP, Jenei K, Prasad V. Regulatory decisions diverge over aducanumab for Alzheimer's disease. ***BMJ*** 2022; 376: e069780.
12. UAE second country globally to grant approval for first and only drug for treatment of early stages of Alzheimer's disease. Published March 10, 2021. Accessed October 17, 2022. https://www.wam.ae/en/details/1395302976448
13. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. ***N Engl J Med*** 2023; 388: 9-21.
14. Tayeb HO, Murray ED, Price BH, Tarazi FI. Bapineuzumab and solanezumab for Alzheimer's disease: is the "amyloid cascade hypothesis" still alive? ***Expert Opin Biol Ther*** 2013; 13: 1075-1084.
15. Day GS, Scarmeas N, Dubinsky R, Coerver K, Mostacero A, West B, et al. Aducanumab Use in Symptomatic Alzheimer Disease Evidence in Focus: A Report of the AAN Guidelines Subcommittee. ***Neurology*** 2022; 98: 619-631.
16. Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, et al. Amyloid-Related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients With Early Alzheimer Disease. ***JAMA Neurol*** 2022; 79: 13-21.
17. Salloway S, Chalkias S, Barkhof F, Burkett P, Barakos J, Purcell D, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. ***Alzheimers Res Ther*** 2021; 13: 80.
18. Mintun MA, Lo AC, Evans CD, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in Early Alzheimer's Disease. ***N Engl J Med*** 2021; 384: 1691-1704.
19. Shcherbinin S, Evans CD, Lu M, Andersen SW, Pontecorvo MJ, Willis BA, et al. Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial. ***JAMA Neurol*** 2022; 79: 1015-1024.
20. Zimmer J, Solomon P, Evans CD, Lu M, Sims JR, Brooks DA, et al. TRAILBLAZER-ALZ 2: A Phase 3 Study to Assess Safety and Efficacy of Donanemab in Early Symptomatic Alzheimer's Disease (P18-3.005). ***Neurology*** 2022; 98: 1688.
21. Roche provides update on Phase III GRADUATE programme evaluating gantenerumab in early Alzheimer's disease. Roche Press Release November 14, 2022. https://www.roche.com/media/releases/med-cor-2022-11-14
22. Andrews JC, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. ***Alzheimers Dement (N Y)*** 2019; 5: 354-363.
23. Arenaza-Urquijo EM, Bejanin A, Gonneaud J, Wirth M, La Joie R, Mutlu J, et al. Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: neuroimaging evidence for protection and compensation. ***Neurobiol Aging*** 2017; 59: 72-79.
24. Noroozian M, Shakiba A, Iran-nejad S. The impact of illiteracy on the assessment of cognition and dementia: a critical issue in the developing countries. ***Int Psychogeriatr*** 2014; 26: 2051-2060.
25. Alshammari SA, Alhamdan AA, Bindawas SM, Al-Amoud MM, Al-Orf SM, Al-Muammar MN, et al. Assessing the cognitive status of older adults attending primary healthcare centers in Saudi Arabia using the Mini-Mental State Examination. ***Saudi Med J*** 2020; 41: 1315-1323.
26. Muayqil TA, Alamri NK, Alqahtani AM, Julaidan SS, Alsuhaibani R, Nafisah I, et al. Normative and Equated Data of the Original and Basic Versions of the Montreal Cognitive Assessment among Community Dwelling Saudi Arabians. ***Behav Neurol*** 2021; 2021: e5395627.
27. Alkeridy WA, Muayqil TA, Al Khalifah RA, Mohammedin AS, Khallaf RA, Bucks RS. Arabic translation and cross-cultural adaptation of the Bristol Activities of Daily Living Scale (BADLS). ***Alzheimers Dement*** 2021; 17: e050856.
28. Feghali Y, Fares Y, Abou Abbas L. Assessment of neuropsychiatric symptoms in dementia: validity and reliability of the Lebanese version of the neuropsychiatric inventory questionnaire. ***Appl Neuropsychol Adult*** 2021; 28: 588-595.
29. Alobaidy A, Al-Sinawi H, Al-Asmi A, Al-Adawi S, Essa MM, El-Okl M, et al. CERAD Neuropsychological Battery-Arabic Version: Regression-Based and Stratified Normative Data and Effects of Demographic Variables on Cognitive Performance in Older Omanis. ***Cogn Behav Neurol Off J Soc Behav Cogn Neurol*** 2017; 30: 150-158.
30. Karam GE, Khandakji MN, Sahakian NS, Dandan JC, Karam EG. Validation into Arabic versions of Dementia Rating Scales, Dementia Caregivers Scales, and Dementia Research Instruments. ***Alzheimers Dement Amst Neth*** 2018; 10: 796-801.
31. Ben Jemaa S, Attia Romdhane N, Bahri-Mrabet A, Jendli A, Le Gall D, Bellaj T. An Arabic Version of the Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog): Reliability, Validity, and Normative Data. ***J Alzheimers Dis*** 2017; 60: 11-21.
32. Cummings J, Aisen P, Apostolova LG, Atri A, Salloway S, Weiner M. Aducanumab: Appropriate use recommendations. ***J Prev Alzheimers Dis*** 2021; 8: 398-410.
33. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. ***Neurology*** 2019; 93: e1647-e1659.
34. Sinha P, Barocas JA. Cost-effectiveness of aducanumab to prevent Alzheimer's disease progression at current list price. ***Alzheimers Dement (N Y)*** 2022; 8: e12256.
35. Lam J, Hlávka J, Mattke S. The Potential Emergence of Disease-Modifying Treatments for Alzheimer Disease: The Role of Primary Care in Managing the Patient Journey. ***J Am Board Fam Med*** 2019; 32: 931-940.
36. Hampel H, Au R, Mattke S, Van der Flier WM. Designing the next-generation clinical care pathway for Alzheimer's disease. ***Nat Aging*** 2022; 2: 692-703.