Facing Alzheimer's disease in the developing countries.

Enfrentando la enfermedad de Alzheimer en los países en desarrollo.

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SUMMARY

Although the increase in the Alzheimer's disease (AD) in developed countries will be limited, in the developing countries of Latin America, Asia and Africa, it will be by the year 2050 three times that of the developed countries. That some correlations between AD and risk factors valid for developed countries are not as robust when compared to those in development, suggests differences in drug development. Due to the high cost of medicines from industrialized countries, it is doubtful that AD treatment would be a priority in the developing ones; thus, a better strategy would be to prevent or delay the disease. Of the options, the AD vaccine is the most favorable despite that all the attempts to develop it have failed, a result of products developed using inadequate information, which have fostered a negative opinion of this vaccine. Yet, the available information shows that these vaccines' antigens probably induced a detrimental immunity and that the inflammatory response elicited by some of them aggravated the onset of AD. Because of immunosenescence and the irreversible damage caused by AD, it is doubtful that vaccines would have practical value in treating advance disease. Yet, the available information provides basis for designing vaccines to prevent and/or retard this disease; information that has been ignored and the vaccines to prevent AD in fact discarded. Nonetheless, there is now a good understanding of the antigens needed to induce a protective immunity and the adjuvants required to stimulate production of protective antibodies while suppressing harmful inflammatory immune responses. Considering the limited choices that the developing countries have to control the AD epidemic, it would be sound if they collaborate and use the available knowledge to develop vaccines to prevent/delay AD. This development would yield both medical and economic benefits for Latin America, as well as other regions of the world.

KEYWORDS: Alzheimer's disease, prevention, risk factors, vaccines, amyloid beta, developing countries.

RESUMEN

Aunque el incremento de casos de enfermedad de Alzheimer (EA) en los países desarrollados será limitado, en los países en desarrollo de América Latina, Asia y África será en el año 2050 tres veces el de los países desarrollados. Que ciertas correlaciones entre la EA y factores de riesgo válidas para los países desarrollados no son tan categóricas cuando se aplican a los países en desarrollo, sugiere diferencias en el desarrollo de fármacos para esta enfermedad. Es improbable que, debido al costo de las medicinas de los países industrializados, el tratamiento de la EA sea una prioridad en los países subdesarrollados; por lo tanto, una estrategia más efectiva sería el prevenir o retrasar esta enfermedad. De las opciones, la vacuna contra la EA es la más favorable a pesar de que todos los intentos para producirla han fracasado, resultado de productos desarrollados usando información insuficiente; lo que ha fomentado una opinión negativa de esta vacuna en los círculos científicos. Sin embargo, la información disponible revela que

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los antígenos de esas vacunas posiblemente indujeron una inmunidad perjudicial y que la respuesta inflamatoria estimulada por varias de esas vacunas agravó el inicio de EA. Además, debido al daño irreversible causado por la EA y la inmunosenescencia, es poco probable que las vacunas terapéuticas tengan valor práctico en el tratamiento de la EA en estado avanzado. Sin embargo, esta información provee bases sólidas para diseñar nuevas vacunas para prevenir o retardar esta enfermedad; información que ha sido ignorada y las vacunas para prevenir la EA, de hecho descartadas. No obstante, ahora hay un mejor conocimiento de los inmunógenos necesarios para inducir una inmunidad protectora y de los adyuvantes requeridos para estimular la producción de anticuerpos protectores e inhibir la inmunidad inflamatoria perjudicial. Considerando las opciones limitadas que tienen los países en desarrollo para controlar la epidemia de EA, sería razonable si estos países colaboraran y usaran los conocimientos disponibles para desarrollar vacunas para prevenir/retrasar la EA. Un avance que produciría beneficios médicos y económicos para América Latina y otras regiones del mundo.

PALABRAS CLAVE: Alzheimer, prevención, factores de riesgo, vacunas, amiloide beta, países en desarrollo.

Alzheimer's disease (AD), a neurodegenerative condition associated with aging and the most common type of dementia, can be considered the epidemic of the 21st century. Paradoxically, AD is an unexpected consequence of our longer lifespan, result of medical advances that have curtailed infectious diseases, malnutrition and other health problems. Surprisingly, recent studies have shown that while the developed countries, perhaps due to better medical care would have in the future a limited increase or even a decrease in AD cases, the less wealthy countries would have a dramatic upsurge that by year 2050 may be 3-fold that of the wealthier countries, i.e. over 125 million cases (1). However, it is alarming that the symptoms of AD in Latin Americans appear on the average 7 years earlier than in non-Latino white Americans, and that they have a higher incidence of diabetes, one of the AD risk factors (2).This critical situation is aggravated by the lack of new diagnostic methods and the limited resources available to combat this disease in most Latin American countries (3). But, the prevalence of AD across South America shows large variations, apparently the result of a combination of factors like age, genetics and life style (4). Indeed, the prevalence of AD can be as high as 11.5% in Argentina and as low as <1% in Uruguay and rural Peru, with several countries having values that fall between those limits (4). An important consequence of the AD epidemic, is that due to the high costs of long-term caring for Alzheimer's patients, besides causing a health crisis, it may also impair the developing countries' economies, affecting their progress. Yet, it is doubtful that due to economic reasons, many of the AD preventive and therapeutic products currently under consideration might be readily available in low and some middle-income countries to limit this disease's impact.

Considering the cost of producing some promising biologics like monoclonal antibodies (mAbs) and their administration (5), it is possible that if successful, because of financial constraints their availability may be limited even in the more affluent countries; a situation that would be worse in the less wealthy ones. Indeed, the US average yearly cost of treating a patient with one of the top nine mAbs is $200,000, which is high even for the well-developed countries (6). Thus, the challenge to help developing countries to fight AD without devastating their health care systems is to provide effective pharmaceutical products that would be affordable and easy to administer. Although it has been assumed that new technological advances would bring down the price of drugs like mAbs, those potential reductions in cost while acceptable in wealthier countries would not be adequate for the less wealthy ones. Indeed, important advances like the use of serum-free media and hollow-fiber reactors, due to the complexity of the preparative process, may not contribute to significantly lower the manufacturing costs of products targeting the developing countries. Yet, from the practical point of view and considering the magnitude of the AD epidemic, an approach in which initially some cost-effective methods are used to prevent/delay the onset of the disease, which may at a later point be replaced by therapies such as mAbs, makes sense both medically and financially. However, we can also conclude that in most developing countries due to the economic realities, AD prevention and/or treatment with mAbs and other expensive drugs will be an unlikely choice, a situation that leaves very few viable options.

Different from the US and Europe where AD diagnosis usually involves brain imaging

and evaluation of biomarkers done in special institutions, in Latin Americathe diagnosis of AD is principally done clinically using detailed cognitive or neuropsychometric assessments, offered mainly in private institutions (3,7). Although there are problems with that method due to language, education, and other factors, it is useful in the absence of brain imaging. Yet, this test cannot differentiate dementia due to AD from vascular dementia; with AD being the prevalent one; but, both types of dementia can coexist (7). The usefulness of such evaluation was shown by a study where those with possible dementia, were followed by physical and neurological examinations to determine their cognitive functions and finally by laboratory tests and brain computed tomography (8). This study was able to differentiated between the different types of dementia, where AD was the most prevalent. As indicated initially, the focus of this article will be AD, where amyloid-β (Aβ) has a crucial role, rather than vascular dementia. While, early diagnostic methods to detect AD, like the brain imaging tests Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI), are significantly more accurate, their cost in some developing countries could be the equivalent or more of an average monthly salary. Indeed, a retrospective study of the cost of medical care of dementia patients in Lima, Peru, has shown that their regular monthly medical care, without brain imaging tests, cost 2.5 times the minimum legal monthly wage (9). While some developments are taking place using imaging technologies, such as the Argentina Alzheimer's Disease Neuroimaging Initiative (10), it is dubious that due to economic limitations those diagnostic centers may be readily available in most developing countries. An alternative approach, currently in the validation phase, would be the use of biomarkers to predict, e.g. apolipoprotein E4 (ApoE4) genotype, or diagnose early AD, like the levels of amyloid-β_{42} (Aβ42), tau and other biomarkers in cerebrospinal fluid (10) or serum; analyses that can be perform in most clinical laboratories without the need for expensive instrumentation and reagents. In fact, it has been reported that the presence in serum of two biomarkers, IL-18 and protein I-309, was highly specific for elderly Hispanics with AD or mild cognitive impairment (11); results that were influenced by the race and ethnicity of the population.

Considering the complexities of AD, it is doubtful that there will be a cure or even an effective treatment for this disease in the near future; thus, a new strategy is to develop drugs that prevent and/or delay this disease onset or progression. An endeavor that would require the identification of risk factors or indicators of incipient disease to initiate treatment. That early AD diagnosis using brain imaging would be unlikely in most developing countries, means that preventive treatments based mostly on risk factors, would need to take place at an age that statistically is earlier than that where this disease starts to emerge. However, due to the presumably large number of people eligible for preventive treatment, i.e. those 55 years of age and older, the medications must be affordable, have minor side effects if any and their administration should not require hospitalization to avoid overwhelming those countries' medical institutions. Other factors would be minimal cold chain requirements and good stability to have products with dependable long-term properties; all conditions that could lessen the accessibility to most biologics. Hence, the successful products in developing countries would be most likely small synthetic drugs like BACE inhibitors (12,13), and preventive vaccines that although considered biologics have cost-effective manufacturing processes and good stability (14). Yet, because of the intricate AD etiology, a combination of different methods, e.g. BACE inhibitors plus AD vaccines, could be an effective option. While several of the drugs under development would intervene at different therapeutic targets, their prescription might require establishing the patient's genetic risk factors (15); a procedure that due to cost may be another limiting matter in low income countries. The other viable option, preventive vaccination, takes advantage of the natural protective anti-AD immunity that appears early in life but declines with advanced age when AD starts to appear (16); of relevance is that vaccines' efficacy is seldom dependent on genetic factors, as shown by the infectious disease vaccines. Moreover, passive immune therapy with aducanumab, copy of a naturally present protective anti-Aβ antibody found in elderly but mentally healthy people, has shown to be effective regardless of the individual's ApoE4 status (17), which confirms both the presence of a natural anti-AD protective immunity, the independence of the immune response from genetic factors. However, despite of the natural protective immunity, which is usually an indication of successful vaccine development, all the attempts to develop effective anti-AD vaccines have ended in failures.

A result of those disappointments has been the premature conclusion that AD vaccines may be unfeasible because of a questionable sustaining science (18); an opinion that would eliminate vaccines as an alternative to control this epidemic. This viewpoint

"appears" to be supported by the failures of most mAbs, which while not recognizing the pathogenic Aβ small oligomers crucial in AD pathology, recognize the normal and harmless monomers. In contrast, the promising results obtained with aducanumab, a mAb that targets the neurotoxic oligomers and evidently protects against cognitive decline in humans, strengthens the notion of a natural anti-AD protective immunity (19). Further support for a protective anti-AD immunity is given by a retrospective study showing that prior treatment of cognitively healthy individuals with IV immunoglobulins resulted in 42% lower risk of developing AD after 5 years of treatment (20). So, why despite the evidence supporting a natural protective immunity, the AD vaccine development has been a continuous disappointment? An examination of this vaccine's advancement indicates that the formulations developed using the incomplete information available at that time, were inadvertently inducing a likely damaging rather than protective immune response; which would explain their failure. Indeed, while those vaccines induced an immunity that removed the Aβ plaques that are presumed to be associated with AD pathology, apparently, they also released toxic Aβ oligomers that kill the nerve cells (21). Relevant for AD is that neurons do not reproduce like other cells do; thus, neural damage is a cumulative and irreparable event, which explains the exacerbation with time of this disease and raises doubts about successful treatments for advanced AD. Also, new information indicates that plaque rather than being damaging, by sequestering and trapping the neurotoxic Aβ oligomers plays a protective role [Reviewed in 18]. In effect, these vaccines' failures parallel those observed with the clinically tested mAbs, which with the exception of aducanumab, recognized the non-toxic Aβ monomers but not the cytotoxic oligomers. Besides, due to the elderly declining immunity, AD vaccines require adjuvants to improve the immune response (22); yet, depending on the adjuvant, they may stimulate a damaging inflammatory autoimmunity, which can hasten and exacerbate AD. That the available adjuvants largely elicit an inflammatory immune response, presents a major obstacle to AD vaccine development. Consequently, development of preventive AD vaccines would require a strategy that recognizes the unique requirements, which are different from those for infectious diseases and cancer vaccines where the goal is to elicit an inflammatory immune response to destroy the infected or aberrant cells.

Hence, preventive vaccines to control the increase of AD may need, besides boosting the protective natural immunity against the toxic forms of Aβ and proteins like tau that are relevant for this disease's pathology, to ameliorate the age-associated immune decline that interferes with the production of a protective immunity (23). Indeed, requirements that have not been fulfilled by any of the tested Aβ vaccines, which without exception have failed clinically. Then, to be effective, AD vaccines would need antigens that different from the past vaccines direct the immune response to the correct target, i.e. the conformational epitope responsible for Aβ oligomers neurotoxicity, this way preventing a damaging immunity (21). However, to do so these antigens would need to carry both B and T cell epitopes, which may induce a damaging inflammatory cytotoxic response. Hence, these new AD vaccines would require sole anti-inflammatory adjuvants to stimulate the production of protective antibodies by a declining immune system, while inhibiting a damaging inflammatory autoimmunity that may aggravate or accelerate the onset of AD (23). This requisite would be more critical in the less developed countries, where malnutrition and chronic infectious diseases weaken the population's immune systems. While anti-inflammatory adjuvants are rare, some new ones that work at the dendritic cell level should facilitate the development of safe and effective AD vaccines (23,24). In fact, some of these adjuvants are glycosides derived from the bark of *Quillaja saponaria*, a tree native to Peru and Chile (23). Since it is unlikely that due to economic reasons the countries in development could take advantage in the future of effective but costly AD preventive and therapeutic products, preventive vaccination may be an effective way to alleviate the impact of AD on those societies; a situation reminiscent of that for the infectious disease vaccines. In fact, according to studies by organizations like the Alzheimer's Research UK and Alzheimer's Association in the US (1,25), a delay of 5 years in the onset of AD by 2050 would reduce the incidence of AD between 30 and 40 percent as well as the expenses associated with the care of the affected population.

Several epidemiological studies forecast that Latin America/Caribbean would be among the hardest hit regions by the AD epidemic; with some studies estimating that Latin America that currently accounts for near 10% of the global sporadic AD cases (26), will double that number by 2030 (1). Hence, the consensus is that the increase of AD in Latin America is larger than that observed in other parts of the world. Indeed, while in the year 2010 the cost of dementia in Latin America was $23,000 million, it increased to nearly $46,000 million by year 2015 (1). Attempts to correlate certain risk factors like ApoE4 with the incidence of AD in

Latin America has not shown the robust link observed in Asia, Europe and the US (27,28). Indeed, recent studies show that in certain ethnic groups from South America, EpoE4 under some conditions like high parasite burden may ameliorate the effects of AD; a situation that demonstrates the role of environmental issues in modifying risk factors (29) and that reflects the complex racial and socioeconomic diversity of this region. Actually, the only factors that seem to closely correlate with sporadic AD in Latin America are age and the degree of education, which also compare well in other parts of the world (30). However, that the degree of education usually correlates with socioeconomic status and better healthcare, makes the interpretation rather complex. Yet, regardless of the various factors involved, that Latin America has one of the world's fastest growing elder population would explain the rapid increase in AD; i.e. equal or faster than that of the US at the present. But, different from the US and other wealthier countries, many countries in Latin America as well as in Asia and Africa do not have the economic or the medical resources needed to confront this unexpected increase in AD. Hence, it is possible that a lack of access to affordable anti-AD preventive products would disturb the economies of some developing countries, leading to a disruption of their social fabric and declining of the socioeconomic advances made during the recent decades. However, considering the apparent differences between the impact of AD risk factors in Latin America and the US/Europe, as well as the economic disparities, it is unlikely that the development of preventive drugs targeted to the less developed countries would be a high priority in the more affluent ones. A situation that has been muddled by the consistent failures of the efforts to develop AD vaccines, which has led the pharmaceutical industry and research institutions to abandon that approach, despite of the new information that identifies the most likely but unbeknown errors that led to those failures (18,21).

Hence, considering: i) the magnitude of the AD crisis and its impact on the health and economies of the developing countries, ii) the apparent differences in the effects of the risk factors between Latin America and the US/Europe and, iii) the low prospects that pharmaceutical companies or scientific institutions would try to develop in the near future AD preventive products amenable to those countries, it would be reasonable for the Latin American countries to join forces to develop those critically needed products. In fact, ever since the disappointing results of the past AD vaccines, a large body of information regarding various issues with these vaccines has been gathered, which would allow for their rational design. For example, there is a more accurate image of the antigens needed to induce a safe protective immunity; there is a very good understanding for the need of sole anti-inflammatory adjuvants, which are now available, and finally there is the recognition that AD vaccines should be used in a preventive mode while the immune system is still competent, rather than in a therapeutic one when it may be too late. In fact, it is now well accepted that like with cancer, AD occurs when the immunity starts to decline due to immunosenescence. Consequently, and as predicted by several models, it is possible to assume that a cost-effective vaccine capable of preventing or delaying the onset of AD would result in significant medical and financial benefits to Latin America and other regions.

REFERENCES

1. Prince MJ. World Alzheimer Report 2015: The Global Impact of Dementia. London: Alzheimer's Disease International; 2015. (Accessed 2 May 2017) Available from: https://www.alz.co.uk/research/world-report-2015
2. Snyder HM, Cardenas-Aguayo M, Alonso A, Bain L, Iqbal K, Carrillo MC. Alzheimer's research in Ibero America. Alzheimer Dement. 2016; 12:749-754.
3. Baez S, Ibáñez A. Dementia in Latin America: An emergent silent tsunami. Front Aging Neurosci. 2016; 8:253. doi: 10.3389/fnagi.2016.00253
4. Cardona-Gómez, GP, Lopera F. Dementia, preclinical studies in neurodegeneration and its potential for translational medicine in South America. Front Aging Neurosci. 2016; 8:304. doi: 10.3389/fnagi.2016.0034
5. National Research Council (US) Committee on Methods of Producing Monoclonal Antibodies. Monoclonal Antibody Production. Washington DC: National Academies Press (US); 1999.
6. Shaughnessy AF. Monoclonal antibodies: magic bullets with a hefty price. BMJ. 2012; 345: e8346.
7. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management and risk factors. Lancet Neurol. 2008; 7:812-826.
8. Custodio N, García A, Montesinos R, Escobar J, Bendezú L. Prevalencia de demencia en una población urbana de Lima-Perú: estudio puerta a puerta. An Fac med. 2008; 69:233-238.
9. Custodio N, Lira D, Herrera-Perez E, Nuñez del Prado L, Parodi J, Guevara-Silva E, et al. Cost-of-illness study in a retrospective cohort of patients with dementia in Lima, Peru. Dement Neuropsychol. 2015; 9:32-41.

10. Russo MJ, Cohen G, Mendez PC, Campos J, Nahas FE, Surace EI, et al. Predicting episodic memory performance using different biomarkers: results from Argentina-Alzheimer's disease neuroimaging initiative. Neuropsychiatr Dis Treat. 2016; 12:2199-2206.
11. Villareal AE, O'Bryant SE, Edwards M, Grajales S, Britton JP, Panama Aging Research Initiative. Serum-based protein profiles of Alzheimer's disease and mild cognitive impairment in elderly Hispanics. Neurodegener Dis Manag. 2016; 6:203-213.
12. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. Drug Des DevelTher. 2013; 7:1471-1478.
13. Cazarim MdS, Moriguti JC, Ogunjimi AT, Pereira LRL. Perspectives for treating Alzheimer's disease: a review on promising pharmacological substances. Sao Paulo Med J. 2016; 134:342-354.
14. Marciani D. Alzheimer's disease: Toward the rational design of an effective vaccine. Rev Neuropsiquiatr. 2015; 78(3):140-152.
15. Williamson J, Goldman J, Marder KS. Genetic aspects of Alzheimer's disease. Neurologist. 2009; 15: 80-86.
16. Britschgi M, Olin CE, Johns HT, Johns HT, Takeda-Uchimura Y, LeMieux MC, et al. Neuroprotective natural antibodies to assemblies of amyloidogenic peptides decrease with normal aging and advancing Alzheimer's disease. Proc Natl Acad Sci USA. 2009; 106: 12145-12150.
17. Jeffrey S. More positive data on aducanumab in Alzheimer's. Washington: Medscape; 2015.
18. Marciani DJ. Rejecting the Alzheimer's disease vaccine development for the wrong reasons. Drug Discov Today. 2017;22(4):609-614. doi: 10.1016/j.drudis.2016.10.012
19. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M,et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease.Nature. 2016; 537:50-56.
20. Fillit H, Hess G, Hill J, Bonnet P, Toso C. IV immunoglobulin is associated with a reduced risk of Alzheimer's disease and related disorders. Neurology. 2009; 73:180-185.
21. Marciani DJ. A retrospective analysis of the Alzheimer's disease vaccine progress: The critical need for new development strategies. J Neurochem. 2016; 137:687-700.
22. Bergmann-Leitner ES, Leitner WW. Adjuvants in the driver's seat: How magnitude, type, fine specificity and longevity of immune responses are driven by distinct classes of immune potentiators. Vaccines. 2014; 2: 252-296.
23. Marciani DJ. New Th2 adjuvants for preventive and active immunotherapy of neurodegenerative proteinopathies. Drug Discov Today. 2014;19(7):912-20.
24. Marciani DJ. Alzheimer's disease vaccine development: A new strategy focusing on immune modulation. J Neuroimmunol. 2015; 287:54-63.
25. Alzheimer's Association. Changing the trajectory of Alzheimer's Disease Report 2015. Chicago: Alzheimer's Association National; 2016
26. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. BioMed Res Int. 2014;2014:908915. doi: 10.1155/2014/908915.
27. Paz-y-Miño C, García-Cárdenas JM. Alzheimer's disease in Latin America and Caribe. En: SMGroup. Alzheimer's Disease. Dover: SMGroup; 2016. (Accessed 2 May 2017) Available from: http://www.smgebooks.com/alzheimers-disease/chapters/ALZD-15-02.pdf
28. Sadigh-Eteghad S, Talebi M, Farhoudi M. Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer`s disease. A meta-analysis. Neurosciences (Riyadh). 2012; 17:321-326.
29. Trumble BC, Stieglitz J, Blackwell AD, Allayee H, Beheim B, Finch CE, et al. Apolipoprotein E4 is associated with improved cognitive function in Amazonian forager-horticulturalists with a high parasite burden. FASEB. 2016. 31(4): 1508-1515. doi: 10.1096/fj.201601084R
30. Nitrini R, Bottino CMC, Albala C, Capuñay NSC, Ketzoian C, Rodriguez JJL et al. Prevalence of dementia in Latin America: a collaborative study of population-based cohorts. Int Psychogeriatr. 2009; 21:622-630.

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