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Bapineuzumab

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Abstract

Importance of the field—Alzheimer’s disease is the leading cause of dementia in the elderly, and there is no disease-modifying therapy yet available. Immunotherapy directed against the β -amyloid peptide may be capable of slowing the rate of disease progression. Bapineuzumab, an anti- β -amyloid monoclonal antibody, will be the first such agent to emerge from Phase III clinical trials.

Areas covered in this review—The primary literature on bapineuzumab from 2009–2010 is reviewed in its entirety, along with the literature on AN1792, a first-generation anti- β -amyloid vaccine, from 2003–2009. Other Alzheimer’s disease immunotherapeutics currently in development, according to www.clinicaltrials.gov, are also discussed.

What the reader will gain—In addition to a critical appraisal of the Phase II trial results for bapineuzumab, this review considers the broader field of immunotherapy for Alzheimer’s disease as a whole, including the challenges ahead.

Take home message—Bapineuzumab appears capable of reducing the cerebral β -amyloid peptide burden in patients with Alzheimer’s disease. However, particularly in *APOE* ϵ 4 carriers, its ability to slow disease progression remains uncertain, and vasogenic edema — a dose-limiting and potentially severe adverse reaction — may limit its clinical applicability.

Keywords

Alzheimer’s disease; β -amyloid peptide (amyloid- β A β); Bapineuzumab; Immunotherapy (immunization); Monoclonal antibody; Vasogenic edema

1. INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of age-related cognitive decline, currently affecting 5.3 million Americans at a cost of \$148 billion per year (Alzheimer’s Association, www.alz.org). Bapineuzumab (AAB-001; Janssen/Elan/Pfizer), a humanized monoclonal antibody targeting the β -amyloid peptide (A β), is currently in Phase III clinical trials for the treatment of AD (Box 1) [1]. This agent is furthest along in a competitive field for passive A β immunotherapy, and there is a lot at stake: The future direction of AD

therapeutics — and indeed the basic hypothesis that clearance of A β plaques will slow the progression of Alzheimer's disease — may hinge on bapineuzumab's outcome.

Box 1

Drug Summary

Drug name	Bapineuzumab
Phase	III
Indication	Alzheimer's disease
Pharmacology	Humanized monoclonal IgG1 antibody against the β -amyloid (A β) N-terminus(A β ₁₋₅), based on the murine antibody 3D6 and intended to promote A β clearance from the brain
Route of administration	Intravenous
Pivotal trials	Phase II [1,53], Phase III (NCT00575055 and NCT00574132)

2. A β IMMUNOTHERAPY

Ever since the discovery that A β is the major constituent of amyloid plaques in AD and that familial AD results from mutations in the gene for amyloid precursor protein (APP) or in genes responsible for processing APP to A β [2], there has been a push to develop anti-amyloid therapeutics. Driven in part by the success of antibody therapies to target and destroy tumor antigens in neoplastic disease, and by the absence of competition from less costly small molecules, immunotherapy against A β emerged as the industry's best hope for the first marketable disease-modifying agent for AD. A brief review of this field is helpful before considering the specific case of bapineuzumab.

2.1. Preclinical studies

Schenk and colleagues were the first to show that in mice overexpressing a mutant, disease-causing allele of human APP, immunization with A β markedly reduced cerebral A β plaque accumulation [3]. Immunized mice showed improved performance on behavioral tests of cognition [4,5], and similar findings were reported when mice received passive immunization with peripherally-administered anti-A β antibodies [6,7]. Despite some reservations about the relevance of mouse models for human disease, the near-disappearance of plaques with A β immunotherapy, replicated now by several other groups [8–13], is visually and intellectually tantalizing.

2.2. Active Immunization in Humans

These exciting preclinical studies spurred the early development of an A β vaccine. AN1792 (Elan/Wyeth), a preparation of aggregated, synthetic, full-length (42-amino acid)human A β ₁₋₄₂ peptide administered with the immune adjuvant QS-21, underwent a successful Phase I study in which a majority of the participants developed an anti-AN1792 titer of at least 1:1000 [14]. In a Phase IIa trial of AN1792 plus adjuvant, 19.7% of 300 subjects responded with a target titer of 1:2200 or greater. Unfortunately, the development of meningoencephalitis in 18 patients (6%) led to an early interruption of the trial [15,16]. This meningoencephalitis occurred only in the treated group, although its incidence did not correlate with antibody titer [16]; in fact, five of these 18 patients were nonresponders who never achieved the target titer threshold. In two patients with meningoencephalitis, neuropathology revealed evidence of T-cell and mononuclear cell-mediated inflammation [17,18].

Neuropathology yielded another important finding — the vaccine appeared to work [17–20]: Cortical plaque burden was conspicuously low in comparison to neurofibrillary tangles and amyloid angiopathy, not only in patients who had developed meningoencephalitis (perhaps an overly vigorous immune response) [17,18], but also in patients followed long-term who had no clinical signs of a neuroinflammatory adverse reaction [19,20]. Supporting the hypothesis that the vaccine was responsible, plaque burden correlated inversely with titer, and the two patients with the highest titers had almost no cortical amyloid [19]. Thus, vaccination with A β seemed to achieve what it had set out to do — to facilitate clearance of plaques from the brain.

The clinical response to AN1792 was less robust. In patients from the Phase IIa study followed for a mean of 4.6 years, caregivers did endorse less functional decline on the Disability Assessment for Dementia (DAD) and the Dependence Scale for patients achieving the target antibody titer of $\geq 1:2200$ relative to placebo [21]. However, the groups did not differ in the proportions housed at home versus long-term care facilities, in the Clinical Dementia Rating– Sum of Boxes(CDR-SB), or in a variety of objective neuropsychological and cognitive measures. Amongst patients followed to death from the Phase I study, no statistically significant effect emerged with respect to survival or time to the development of severe dementia [19]. Indeed, of the eight patients examined at autopsy, seven — including the two whose brains were nearly devoid of plaques — had unmeasurable Mini Mental State Examination (MMSE) scores at the time of death [19].

There are several possible explanations for this clinicopathological discrepancy: Least likely is that AN1792 itself caused neurodegeneration, as the clinical course for treated and untreated patients was so similar. Perhaps A β had already exerted its toxic effects at the time of immunization, setting in motion an irreversible cascade that might be prevented only by earlier treatment [22]. Another explanation has to do with an abundance of evidence that A β is most toxic not in its polymeric fibrillar form, but rather as soluble oligomers [23]; it is not clear to what extent AN1792 binds and clears oligomeric A β . Finally, some are now arguing that the A β hypothesis has been wrong all along [24].

2.3. A Passive Alternative

The 6% incidence of meningoencephalitis precluded further clinical development of AN1792 [15]. One strategy that permits more direct control over the extent of the immune response against A β is passive immunization, a topic reviewed recently in this journal [25]. As noted above, passive immunization worked as well as active immunization at reducing A β burden and improving cognition in a mouse model of AD [6–13].

One conceptual hurdle to passive immunization is the blood-brain barrier, and the notion that peripherally administered antibodies may not have access to the tissue of interest. Addressing why passive immunization nevertheless appeared to work in mice, one study reported a massive increase in the plasma concentration of A β , along with the observation that the antibody did not appear in association with A β plaques in the brain [7]. Similar increases in plasma A β that paralleled plasma bapineuzumab levels were observed in the Phase II human study [26]. Other work also suggested that monoclonal antibodies to A β do not accumulate substantially in the brain [27]. Thus was born the “peripheral sink” hypothesis, that circulating antibodies to A β shift the equilibrium of the peptide from the cerebrospinal fluid (CSF) to the plasma, indirectly reducing the brain’s A β burden [7]. Perhaps it is this shift in equilibrium that is critical for improved cognitive performance observed in treated mice, rather than the elimination of plaques [28]. Finally, it remains possible that intravenously-administered antibodies may nevertheless bind A β directly in the brain [29].

Another advantage of passive immunotherapy is the possibility of using monoclonal antibodies — especially helpful when some epitopes of a peptide turn out to be better targets than others. One lesson of AN1792 was that the meningoencephalitis appeared to be T-cell-mediated [17,18]. Whereas antibodies recovered from the serum of AN1792-treated patients mainly reacted against N-terminal epitopes of A β _{1–42} [30], T-cells reacted mainly against mid-region and C-terminal epitopes [31].

These considerations led to the development of bapineuzumab, the prototypical monoclonal antibody against the A β N-terminus.

3. OVERVIEW OF THE MARKET

The potential market for a disease-modifying therapy for AD is vast. Recent estimates put the prevalence of AD in the United States at 5.3 million, with a majority of cases occurring after age 65 (Alzheimer's Association, www.alz.org). As the elderly segment of the population grows, this prevalence will rise.

3.1. Currently Approved Therapies

There are five medications currently FDA-approved for the treatment of AD: tacrine (Cognex[®]; Sciele), donepezil (Aricept[®]; Pfizer), rivastigmine (Exelon[®]; Novartis), galantamine (Razadyne[®]; Ortho-McNeil-Janssen), and memantine (Namenda[®]; Forest). Donepezil, rivastigmine, and galantamine are cholinesterase inhibitors. As successors to tacrine, a first generation compound rarely prescribed because of the potential for hepatotoxicity, they are roughly equally efficacious at providing symptomatic improvement of cognition and function at all stages of AD [32]. Memantine is a low-affinity, use-dependent *N*-methyl-D-aspartate glutamate receptor antagonist that offers similar benefits, but only in moderate to severe AD [33]. The clinical effects of these compounds are small and impermanent, and there is currently no conclusive data to support their use as disease-modifying agents (but see [34,35]).

3.2. Other A β Immunotherapies in Development

Bapineuzumab has competitors, as at least four other companies have monoclonal anti-A β antibodies in various stages of development (Table 1). Its closest competitor is solanezumab, or LY2062430 (Eli Lilly; clinicaltrials.gov identifier NCT00905372). This monoclonal antibody, a humanized version of the mouse antibody m266, raised against A β _{13–28} [36,37], differs from bapineuzumab in at least three ways: First, by recognizing a distinct epitope in the central portion of the peptide, it is able to recognize various N-terminal truncation species (such as A β _{3–42}) that are known to exist alongside full-length A β _{1–42} in AD plaques [38]. It is not known whether this characteristic will influence the clinical efficacy of solanezumab relative to bapineuzumab. Second, whereas bapineuzumab binds amyloid plaques more strongly than soluble A β , solanezumab selectively binds to soluble A β with little to no affinity for the fibrillar form [39]. Third, in small Phase I (N = 19 solanezumab-treated patients) and Phase II (N = 52) studies [37,40], there was no clinical, CSF, or magnetic resonance imaging (MRI) evidence of meningoencephalitis or vasogenic edema, the latter of which has plagued bapineuzumab (see section 4.2.1. below). There is also evidence from the preclinical literature mice treated with m266 are less prone to cerebral microhemorrhage than mice treated with the murine equivalent of bapineuzumab [41]. Unfortunately, the Phase II trial for solanezumab revealed no effect of the treatment on the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) or on retention of the amyloid radiotracer carbon-11-labelled Pittsburgh compound B (¹¹C-PiB; see also section 4.1.4.) and thus no evidence for a therapeutic benefit [40]. A Phase III trial for

solanezumab is now underway, with a planned completion date of July, 2012, approximately one year after bapineuzumab's Phase III trials are slated to end.

Other monoclonal antibodies against A β reportedly exhibit properties distinct from bapineuzumab (Table 1). For instance, PF-04360365 (Pfizer; NCT00722046) targets the free carboxy-terminus of A β _{1–40}, specifically A β _{33–40} [42], and is in Phase II trials. Although its epitope is not published, MABT5102A (Genentech; NCT00736775), in Phase I, distinguishes itself by binding to A β monomers, oligomers, and fibrils with equally high affinity [43]. Information regarding GSK933776A (GlaxoSmithKline; NCT00459550) and gantenerumab (R1450, or RO4909832; Hoffmann-La Roche; NCT00531804), both in Phase I, is not yet publicly available.

Anti-A β antibodies occur naturally in pooled preparations of intravenous immunoglobulin (IVIg or IGIV) [44], which is already FDA-approved for the treatment of a variety of other neurological conditions. Preliminary work showed that IVIg treatment may be efficacious in the treatment of AD [45,46], and advantages to this approach include that IVIg already has a long clinical track record, it is generally safe and well-tolerated, and it circumvents the high research and manufacturing costs associated with monoclonal antibodies. One potential disadvantage is the reliance on human blood donation; increasing demand for IVIg for other indications has already led to periodic shortages. There are two trials currently underway for IVIg in AD, a Phase III trial sponsored by Baxter and the NIH Alzheimer's Disease Cooperative Study (NCT00818662), and a Phase II trial by Octapharma (NCT00812565).

Finally, the game is not yet over for active A β immunization [31]. Avoiding both the strong Th1 effects of QS-21 adjuvant and the T-cell epitopes at the C-terminus of A β , CAD106 (Novartis; NCT00795418) consists of a short N-terminal fragment of A β (A β _{1–6}) attached to a virus-like particle, with no additional adjuvant. This agent is currently in Phase II trials. Also in Phase II is ACC001 (Wyeth; NCT00498602), a vaccine incorporating A β _{1–7}, administered with QS-21 adjuvant. UB311 (United Biochemical; NCT00965588), in Phase I, incorporates a longer N-terminal fragment, A β _{1–14}. Merck's vaccine, V950 (NCT00464334), is also in Phase I. Using a novel approach, Affiris is testing short, six-amino peptides that mimic the free N-terminus of A β and cause cross-reactivity against the native peptide [47]. Two of these so-called "affitope" peptides, AD01 and AD02, were administered with aluminum hydroxide as adjuvant in Phase I trials (NCT00711139 and NCT00711321).

4. BAPINEUZUMAB

This humanized version of the mouse monoclonal antibody 3D6 recognizes A β _{1–5} [48]. It is specific for the A β peptide, and does not cross-react with APP or its α -secretase product [48]. Based on unpublished beneficial effects in the Phase I study, the initial Phase II study included primary efficacy outcomes [1]. A total of 234 patients with a clinical diagnosis of probable AD, aged 50–85 with MMSE scores 16–26, received intravenous bapineuzumab or placebo (vehicle alone) at an 8:7 ratio. Treated patients initially entered into three dosing cohorts: 0.5 mg/kg, 1.0 mg/kg, and 2.0 mg/kg. After evidence of vasogenic edema emerged in patients enrolled in the Phase I study (see section 4.2.1. below), an additional 0.15 mg/kg dosing cohort was added. Based on a half-life of 24 days, the study drug was administered as an IV infusion every 13 weeks, for a total of 6 infusions over 18 months. 65% of patients randomized to bapineuzumab completed the study, as did 71% of placebo-treated patients.

4.1. Efficacy

4.1.1. Cognitive and Functional Outcomes—In the Phase II trial, the two primary outcome measures were the ADAS-Cog and the DAD [1]. In the prespecified efficacy

analysis, using a repeated measures linear mixed effects model, no statistically significant effect of bapineuzumab emerged in a modified intent-to-treat (mITT) population, comprised of patients who received at least one infusion followed by at least one assessment.

Needless to say, these results were disappointing. However, there was a trend towards improved scores on the primary outcome measures, leading the authors to pursue *post hoc* exploratory analyses [1]. To increase statistical power, these exploratory analyses pooled all bapineuzumab-treated patients into a single group, regardless of dose, and a simple comparison of final assessment scores replaced the prespecified model that had assumed a linear rate of disease progression. Still, no statistically significant effect arose in the mITT population. However, in the slightly smaller population of study-completers, significant differences in both ADAS-Cog and DAD, as well as a broader neuropsychological testing battery (NTB), did emerge. The clinical effect was small — there was an approximately 4-point difference between the placebo and bapineuzumab-treated groups on the 70-point ADAS-Cog scale and a 6-point difference on the 100-point DAD at the end of the 78-week trial.

4.1.2. The ApoE4 Effect—Of particular interest was the effect of *APOE* ϵ 4 carrier status on outcomes. ApoE, a protein involved in cholesterol transport in the liver and the brain, occurs in three isoforms: ApoE2, ApoE3, and ApoE4. By an unknown mechanism, ApoE4 is a risk factor for the development of AD [49]. In this Phase II study of bapineuzumab [1], *APOE* ϵ 4 noncarriers in the mITT population exhibited treatment-associated differences in the ADAS-Cog, NTB, MMSE, and CDR-SB (but not on the DAD). By contrast, patients with one or two alleles of *APOE* ϵ 4 showed no treatment effect on any measure.

This disparity in treatment efficacy based on *APOE* ϵ 4 carrier status is one of the main legacies of this Phase II trial [1]. As discussed below, *APOE* ϵ 4 carriers are not only less likely to experience clinical improvement, but they are also more likely to suffer a significant adverse event. The sponsor designed separate Phase III trials for carriers (NCT00575055) and noncarriers (NCT00574132), and it is likely that *APOE* genotyping — currently done mainly in research settings — will become clinically routine.

What underlies this ApoE4 effect? Because vasogenic edema, the most frequent serious adverse event to arise from the Phase 2 study (see 4.2.1. below), was more common in *APOE* ϵ 4 carriers, there were fewer treated carriers than noncarriers in some of the analyses, potentially leading to decreased power to detect an effect. In other words, one hypothesis is that this was just a statistical fluke. Alternatively, since ApoE4 may decrease A β transport across the blood brain barrier [44,49], another hypothesis is that *APOE* ϵ 4 carriers may be resistant to bapineuzumab if it acts primarily by a peripheral sink mechanism. The results from the larger Phase III trials for bapineuzumab, as well as data from competing immunotherapeutic trials (Table 1), may shed further light on this issue.

4.1.3. Biomarker Outcomes: CSF and MRI—Many predict that AD therapeutics will be more effective in the treatment of preclinical patients at risk for AD but with minimal or no cognitive or functional deficits. For this reason, and also because of the desire for a metric less blunt than questionnaires and cognitive tests to track disease progression, there has been great interest in the development of chemical and neuroimaging biomarkers [22]. One of many precedents for the use of such biomarkers in clinical trials is in multiple sclerosis research, where the lesion volume on MRI is frequently used as an outcome measure.

In AD, no biomarker has yet been identified as a useful way to track the success of therapy. In the initial bapineuzumab Phase II trial [1], two candidate biomarkers were studied. First,

the levels of CSF A β and tau, a microtubule-associated protein, were measured in a small sub-study of 20 bapineuzumab-treated and 15 placebo-treated patients. In other studies, these CSF biomarkers discriminate AD patients from controls [50]. In the present study, bapineuzumab treatment did not influence CSF A β or tau levels at week 52 compared to baseline [1]. Second, because AD is associated with brain atrophy on MRI [51], brain and ventricular volume were measured in the enrolled patients. Amongst *APOE* ϵ 4 noncarriers, bapineuzumab was associated with significantly less brain volume loss [1]. The result in *APOE* ϵ 4 carriers was less clear, as bapineuzumab was associated with more ventricular enlargement but no change in brain volume. The latter finding aside, it might be significant that the genetic cohort that experienced a better clinical response to bapineuzumab also exhibited better stabilization of brain volume. More sophisticated MRI metrics may offer even better methods of disease tracking [51].

The observed effects of bapineuzumab on CSF tau and brain volume diverge from those of AN1792. In the Phase II study of AN1792, antibody-responders exhibited a small but significantly greater rate of brain volume loss than placebo-treated subjects, despite evidence for a stabilization of cognitive decline in the same subjects [52]. This finding is opposite to what might be expected, or to what was observed with bapineuzumab [1]. In a subgroup of patients who underwent CSF analysis, AN1792 antibody-responders exhibited lower CSF tau levels relative both to their baseline levels, and relative to placebo-treated patients [15], possibly corresponding to a treatment-related reduction in disease activity. As discussed above, bapineuzumab did not have this effect [1]. If not due to differences in trial length, subject numbers, or other such factors, these findings might imply important mechanistic differences between active and passive A β immunotherapeutic strategies.

4.1.4. Biomarker Outcomes: ^{11}C -PiB—In a smaller, subsequent Phase II study of bapineuzumab in the United Kingdom and Finland [53], the extent of ^{11}C -PiB signal on positron emission tomography (PET) was the primary outcome. PiB, a thioflavin analog that binds fibrillar A β , is used as an *in vivo* marker of cortical amyloid plaques [54]. The 19 bapineuzumab-treated patients in the mITT population (pooled from three dosing cohorts, with infusions administered as in the initial Phase II trial [1] described above) exhibited reduced ^{11}C -PiB retention at 18 months compared to baseline, whereas the 7 placebo-treated patients showed more retention compared to baseline. These data suggest that bapineuzumab — like AN1792 [17–20] — reduced the level of A β in the brain. Of note, the bapineuzumab-treated patients may have had more advanced AD than their placebo-treated counterparts, as they had higher baseline ^{11}C -PiB binding, worse functional ability on the CDR-SB, and worse cognition on the NTB. Nevertheless, the ^{11}C -PiB treatment difference persisted even after statistical correction for all three variables. Another finding of the study was that of the 53 individuals screened, 8 failed to meet inclusion criteria because of low baseline ^{11}C -PiB binding, possibly reflecting a good but imperfect correlation between clinical criteria for probable AD and the presence of definite AD pathology. Or perhaps it reflects the fact that the extent of amyloid pathology correlates poorly with clinical measures, potentially limiting the usefulness of this otherwise impressive candidate biomarker [55].

To date, there is only one autopsy reported for a patient in a bapineuzumab trial [56]. This individual, who exhibited extensive ^{11}C -PiB binding at baseline, went on to participate in the Phase II trial [1], from which he withdrew early because of dementia progression. He died 36 months after his ^{11}C -PiB-PET scan and 11 months after his last dose of bapineuzumab. Neuropathology revealed no evidence of an adverse reaction to the treatment, including no meningoencephalitis or hemorrhage. More importantly, although frequent neuritic A β plaques were present in the cortex, there was an unusual dearth of cortical diffuse A β plaques; in addition, the neostriatum, which usually contains frequent diffuse plaques and

showed strong ^{11}C -PiB retention in this patient, had only rare histopathological evidence of A β deposits. These data suggest that bapineuzumab may have caused a long-lasting reduction in diffuse A β plaque burden in this patient [56]. Although it is unclear how generalizable the findings from this single case may be, the possible preference of bapineuzumab for diffuse rather than neuritic A β plaques was unexpected, given a similar efficacy at reducing the burden of both plaque types in mice [39].

4.2. Safety and Tolerability

4.2.1. Vasogenic Edema—The Phase II studies for bapineuzumab [1,53] were haunted by the ghosts of AN1792. In the initial study [1], 12 of 124 bapineuzumab-treated patients developed vasogenic cerebral edema. Half of these developed clinical symptoms, including headache, confusion, vomiting, and gait disturbance. Vasogenic edema was evident as areas of increased T2 signal intensity on MRI, which was obtained at routine intervals throughout the study. These patients all recovered both clinically and radiographically, and six were redosed at a new, lower dose level – 0.15 mg/kg — followed by a titration up to 50% of the original dose. Bapineuzumab was responsible for this adverse event, as it was observed in none of the placebo-treated patients, and it exhibited a clear dose-dependence. Interestingly, it also increased in frequency with increasing *APOE* ϵ 4 gene dose. In the subsequent Phase II study [53], a similar proportion of bapineuzumab-treated patients (2 out of 20, both *APOE* ϵ 4 carriers) developed vasogenic edema.

An approximately 10% incidence of vasogenic edema is not dissimilar from the 6% incidence of meningoencephalitis in AN1792-treated patients [15]. This reaction was not lethal, and no post mortem data has been reported, but there is a strong possibility that the biological basis is related [25]. The association with *APOE* ϵ 4 carrier status, along with the finding that such individuals have higher levels of A β in the walls of blood vessels [57], supports a model in which anti-A β immunotherapy causes inflammation or other changes in the vessel wall, leading to breakdown of the blood-brain-barrier [25]. The *APOE* ϵ 4 association has strong implications, as carriers appear to have the least to gain and the most to lose from bapineuzumab treatment.

Perhaps the most important lesson is that the emergence of vasogenic edema — unsettling though it is — did not result in an early cessation to the trial. Clinical manifestations were generally mild and manageable by withholding or delaying further infusions (although one patient did require treatment with dexamethasone to relieve the edema). Thus, with vigilant clinical care, the risk of vasogenic edema will not necessarily preclude bapineuzumab's safe use.

4.2.2. Other Adverse Reactions—In general, bapineuzumab was well-tolerated [1,53]. Except for vasogenic edema, side effects were non-specific and dose-independent. Of possible concern was the development of deep venous thrombosis (in 4 bapineuzumab-treated patients versus none in the placebo arm) and pulmonary embolism (1 versus 0) [1]. Four deaths occurred — three during and one after the study [1] — and although they all occurred in the bapineuzumab-treated group, these deaths were not related to dose, *APOE* ϵ 4 status, or the presence of vasogenic edema, and all were considered unrelated to treatment by the investigators and by an independent safety monitoring committee.

5. CONCLUSION

Bapineuzumab will be the first of a family of anti-A β monoclonal antibodies to emerge from clinical trials, with a target date of early summer, 2011, for completion of its two Phase III trials. Despite disappointing results on primary clinical efficacy outcomes [1], the Phase II trials did reveal beneficial effects in at least a subgroup of patients, and they yielded some

important insights: First, *APOE* $\epsilon 4$ carriers with AD appear less likely to benefit from bapineuzumab treatment than noncarriers [1]. Second, vasogenic cerebral edema is a potential dose-limiting side effect of bapineuzumab therapy, particularly in *APOE* $\epsilon 4$ carriers [1,53]. Third, like the first-generation A β vaccine AN1792, bapineuzumab appeared to be successful in facilitating clearance of A β from the brain [53,56]. Although not the slam-dunk treatment that it was hoped to be, bapineuzumab still, for now, holds the ball.

6. EXPERT OPINION

The future of bapineuzumab — and of anti-A β therapeutics generally — might hinge on the answer to one question: Is it worth it?

6.1. Clinical Considerations

AD is a menace, and the need for a clinically significant disease-modifying therapy is great. One often-repeated hypothesis is that any such therapy will be more helpful the earlier it is given in the course of the disease. AD pathology is evident in postmortem tissue long before clinical symptoms emerge [58], testifying to the incredible ability of the brain to tolerate damage. The corollary is that by the time symptoms do emerge, pathology is widespread [58], and there may be less to save. Early diagnosis is key, and clinical biomarkers that predict the risk for AD will play a crucial role, in the same way that serum cholesterol levels are now used routinely to identify and track the risk for myocardial infarction or stroke. But in contrast to the statin medications that might be prescribed to a patient with hypercholesterolemia, A β immunotherapies may carry a higher risk of potentially severe side effects. For this reason, a biomarker must achieve a high degree of specificity, so as not to subject otherwise healthy people to harm.

In the real-world clinical setting, risk-benefit calculations will not be straightforward. Take, for instance, the example of a young, asymptomatic *APOE* $\epsilon 4$ homozygote, who has roughly a 12-fold greater risk for developing AD than a noncarrier [49]. Although the Phase II data on bapineuzumab reviewed here [1,53] suggest that this individual would be more likely to suffer vasogenic edema when treated with bapineuzumab, there is a very reasonable (and currently unsubstantiated) possibility that this risk is mitigated in preclinical AD, before vascular A β deposition has peaked. Indeed, this preclinical stage may be an ideal time for bapineuzumab treatment. It will be years before there is adequate data to guide such sensitive decisions.

To get there faster, future trials should focus on patients with few or no symptoms, but with strong risk factors for AD. For bapineuzumab, or any immunotherapy with a potentially serious side effect, identifying a sufficiently specific AD biomarker may be the rate-limiting step to this approach. If an A β immunotherapy emerges that is not associated with neuroinflammatory sequelae, the bar for such specificity will be lower, and it is possible that a safe vaccine, for instance, might be offered to any middle-aged adult with a family history or other soft risk factor for dementia.

Finally, a number of bapineuzumab's direct competitors were specifically designed to decrease the risk of inflammation and vasogenic edema and thus might threaten bapineuzumab's marketability should they turn out to be efficacious. Moreover, if these newer monoclonal antibodies indeed carry a lower risk of vasogenic edema and other serious adverse events, then it may be possible to use them at higher equivalent doses than bapineuzumab, thus increasing their potential efficacy for A β removal.

6.2. Market Considerations

In general, monoclonal antibodies are expensive to manufacture, but have nevertheless generated top profits because of historically generous reimbursements by payers [59]. As a bonus, monoclonal antibodies are immune to generic competition. An optimistic view is that a successful antibody would, when administered chronically, extend survival in AD (there is not yet any evidence to support that this will be the case), thus extending the duration of an illness that is at the same time expected to increase dramatically in incidence. In other words, the growth of the market would be multiplicative.

However, the reality is that, particularly in the current political and economic environment, the healthcare market will not sustain this level of expansion [59]. And if a vaccine (typically administered in fewer, smaller doses) or an oral medication emerges with disease-modifying effects in AD, a monoclonal antibody would likely have to demonstrate sizable advantages either in efficacy or safety in order to survive. Finally, it now appears likely that *APOE* genotyping at baseline and regular MRIs throughout the course of treatment maybe required for any A β immunotherapy linked to a risk for vasogenic edema or inflammation, adding considerably to the cost of therapy. In sum, unless cheaper and safer approaches fail utterly, there is good reason to worry that even if bapineuzumab emerges from Phase III trials with strong evidence for a disease-modifying effect, it may have only a limited window of marketability. At worst, it may amount to little more than an expensive proof of the A β hypothesis.

6.3. The A β Hypothesis

And there's the rub: the A β hypothesis has taken a beating lately [24]. Despite great advances in knowledge, the basic pathophysiology of Alzheimer's disease, including the specific role of A β , remains incompletely understood. Even the assumption that A β possesses no normal physiological function and that its elimination has no untoward effects on brain function is being questioned [60]. And emerging evidence suggests that the relationship between amyloid pathology and Alzheimer's disease is much less specific than originally envisioned: Amyloid plaques are common in healthy, elderly individuals [55], and the AN1792 experience taught us that plaque elimination may have no effect on cognitive decline or death [19]. The distribution of tau pathology in the brain more closely mirrors cognitive decline [58], and recent evidence from mouse models suggests that tau may play a necessary pathogenic role downstream from A β [61]. The central role for A β in familial AD [2] is compelling, and one possibility is that A β is a sort of prime mover in the disease, if not the final effector. This reasoning could bolster the role of A β immunotherapy, as long as it is administered early enough, before A β -independent downstream events take hold. Even if the A β hypothesis emerges unscathed, and scavenging it from the brain prevents cognitive decline, agents such as bapineuzumab that target fibrillar A β [39] may prove less potent than competitors like solanezumab that target soluble A β oligomers in addition to plaques [23,39].

Despite all of this pessimism, the arrival of a first disease-modifying therapy for AD would be a significant advance, and bapineuzumab is a viable contender. It is worth paying close attention to the Phase III results.

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Table 1

A β Immunotherapies in development.

Drug Name	Sponsor	Characteristics		Phase	References
		Epitope *	Isotype		
<i>Monoclonal Antibodies</i>					
Bapineuzumab (AAB-001)	Janssen/Elan/Pfizer	1-5 (free N- terminus)	IgG1	III	[1,53]; NCT00575055 and NCT00574132
Solanezumab (LY2062430)	Eli Lilly	13-28	IgG1	III	[37-40]; NCT00905372
PF-04360365	Pfizer	33-40 (free C- terminus)	IgG2	II	[42,62]; NCT00722046
MABT5102A	Genentech	NP	NP	I	[43,63]; NCT00736775
GSK933776A	GlaxoSmithKline	NP	NP	I	NCT00459550
Gantenerumab (R1450/RO4909832)	Hoffmann-La Roche	NP	IgG1	I	NCT00531804
<i>Intravenous Immunoglobulin</i>					
Gammagard	Baxter; NIH Alzheimer's Disease Cooperative Study			III	[46]; NCT00818662
Octagam	Octapharma			II	NCT00812565
<i>Active Vaccines</i>		<i>Fragment *</i>			
CAD106	Novartis	1-6		II	[64]; NCT00795418
ACC001	Pfizer	1-7		II	NCT00498602
UB311	United Biochemical	1-14		I	NCT00965588
V950	Merck	NP		I	NCT00464334
AD01/AD02	Affiris	**		I	[47]; NCT00711139/NCT00711321

NP, not published

* Numbers correspond to amino acid positions on the A β peptide

** 6-amino acid peptides that mimic the free N-terminus of A β [47]