Antibody Reduces Amyloid-Beta in Alzheimer's

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FROM ARCHIVES OF NEUROLOGY

Treatment with a monoclonal antibody directed against amyloid-beta peptides produced a dose-dependent reduction of amyloid in the brains of patients with Alzheimer's disease in a randomized, placebo-controlled, double-blind study with 16 patients.

While promising, the study's small size limited the results, and the authors acknowledged the continued uncertainty of the clinical significance of amyloid reduction in Alzheimer's disease patients.

"It is still unclear whether any reduction in brain amyloid level will translate into clinical efficacy," wrote Dr. Susanne Ostrowitzki, a researcher at Hoffmann-La Roche in Basel, Switzerland, and her associates (Arch. Neurol. 2011 Oct. 10 [doi:10.1001/archneurol.2011.1538]). "A phase II clinical trial is underway to investigate whether a clinical benefit can be achieved in gantenerumab-treated patients with prodromal Alzheimer disease."

Gantenerumab, the fully-human monoclonal antibody they tested, binds to amyloid-beta plaques. Researchers at Hoffmann-La Roche are testing gantenerumab as a potential therapeutic agent for patients with Alzheimer's disease.

The current study enrolled patients with mild to moderate disease, and compared two to seven intravenous infusions of the antibody, at a dosage of 60 or 200 mg per infusion every 4 weeks, against placebo infusions. The report focused on data collected on a subset of 16 patients from a dose escalation study who underwent measurement of brain amyloid-beta location and amount by positron emission tomography (PET) imaging of

VITALS

Major Finding: Monthly infusion with 200 mg gantenerumab, a monoclonal antibody to amyloid-beta, resulted in an average 15% decline in the amount of brain amyloid-beta in patients with mild to moderate Alzheimer's disease.

Data Source: Randomized trial of 16 patients with mild to moderate Alzheimer's disease given monthly infusions with 60 or 200 mg gantenerumab or placebo for up to seven total infusions.

Disclosures: Dr. Ostrowitzki and several of her coauthors are employees of Hoffmann-La Roche, which supported the study. Two additional coauthors are employees of GE Healthcare.

C^{11}-labeled Pittsburgh Compound B at baseline and following treatment.

At the end of treatment, the four patients in the placebo group had an average increase of 21% in their standard uptake value ratio (SUVR), measured by PET, compared with baseline. The six patients who received 60-mg dosages of gantenerumab had an average increase in SUVR of 5%, and the six patients treated with 200-mg dosages had an average decrease in their SUVR of 15%. The increases and decreases in SUVR appeared consistent across all brain regions examined except in the pons, a region known to have limited amyloid deposition. The effect of the antibody on amyloid deposits appeared rapidly, following two to seven antibody infusions.

The researchers failed to see consistent changes in cognitive measures in patients that correlated with the amyloid changes, but noted that the number of patients was small and the treatment period relatively brief. "Individual changes in cognitive measures did not correlate with changes in levels of amyloid," they wrote.

Additional studies run by the researchers on freshly-harvested human primary microglia cells indicated that phagocytosis was the likely mechanism by which gantenerumab treatment led to reduced amyloid levels. This finding suggests that the antibody, at appropriate dosages, produces reduced amyloid levels without significantly changing vascular permeability by inflammation or by blocking amyloid-beta clearance pathways. ■

Phenylketonurics

VIMPAT oral solution contains aspartame, a source of phenylalanine. A 200 mg dose of VIMPAT oral solution (equivalent to 20 mL) contains 0.32 mg of phenylalanine.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials in patients with partial-onset seizures, 1327 patients have received VIMPAT of whom 1000 have been treated for longer than 6 months and 852 for longer than 12 months.

Clinical Trials Experience

Controlled Trials

Adverse reactions leading to discontinuation

In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive VIMPAT at the recommended doses of 200 and 400 mg/day, respectively, 29% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse events most commonly (>1% in the VIMPAT total group and greater than placebo) leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred.

Most common adverse reactions

Table 2 gives the incidence of treatment-emergent adverse events that occurred in ≥2% of adult patients with partial-onset seizures in the total VIMPAT group and for which the incidence was greater than placebo. The majority of adverse events in the VIMPAT patients were reported with a maximum intensity of 'mild' or 'moderate'.

Table 2: Treatment-Emergent Adverse Event Incidence in Double-Blind, Placebo-Controlled Partial-Onset Seizure Trials (Events ≥2% of Patients in VIMPAT Total and More Frequent Than in the Placebo Group)

System Organ Class/ Preferred Term	Placebo N=364 %	VIMPAT 200 mg/day N=270 %	VIMPAT 400 mg/day N=471 %	VIMPAT 600 mg/day N=203 %	VIMPAT TOTAL N=944 %
Ear and labyrinth disorder					
Vertigo	1	5	3	4	4
Eye disorders					
Diplopia	2	6	10	16	11
Vision blurred	3	2	9	16	8
Gastrointestinal disorders					
Nausea	4	7	11	17	11
Vomiting	3	6	9	16	9
Diarrhea	3	3	5	4	4
General disorders and administration site conditions					
Fatigue	6	7	7	15	9
Gait disturbance	<1	<1	2	4	2
Asthenia	1	2	2	4	2
Injury, poisoning and procedural complications					
Contusion	3	3	4	2	3
Skin laceration	2	2	3	3	3
Nervous system disorders					
Dizziness	8	16	30	53	31
Headache	9	11	14	12	13
Ataxia	2	4	7	15	8
Somnolence	5	5	8	8	7
Tremor	4	4	6	12	7
Nystagmus	4	2	5	10	5
Balance disorder	0	1	5	6	4
Memory impairment	2	1	2	6	2
Psychiatric disorders					
Depression	1	2	2	2	2
Skin and subcutaneous disorders					
Pruritus	1	3	2	3	2

Laboratory abnormalities

Abnormalities in liver function tests have been observed in controlled trials with VIMPAT in adult patients with partial-onset seizures who were taking 1 to 3 concomitant anti-epileptic drugs. Elevations of ALT to ≥3× ULN occurred in 0.7% (7/935) of VIMPAT patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases >20x ULN was observed in one healthy subject 10 days after VIMPAT treatment completion, along with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to VIMPAT.

Other Adverse Reactions in Patients with Partial-Onset Seizures

The following is a list of treatment-emergent adverse events reported by patients treated with VIMPAT in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials. Events addressed in other tables or sections are not listed here. Events included in this list from the controlled trials occurred more frequently on drug than on placebo and were based on consideration of VIMPAT pharmacology, frequency above that expected in the population, seriousness, and likelihood of a relationship to VIMPAT. Events are further classified within system organ class.

Blood and lymphatic system disorders: neutropenia, anemia

Cardiac disorders: palpitations

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: constipation, dyspepsia, dry mouth, oral hypoaesthesia

General disorders and administration site conditions: irritability, pyrexia, feeling drunk

Injury, poisoning, and procedural complications: fall

Musculoskeletal and connective tissue disorders: muscle spasms

Nervous system disorders: paresthesia, cognitive disorder, hypoaesthesia, dysarthria, disturbance in attention, cerebellar syndrome

Psychiatric disorders: confusional state, mood altered, depressed mood

Intravenous Adverse Reactions

Adverse reactions with intravenous administration generally appeared similar to those observed with the oral formulation, although intravenous administration was associated with local adverse events such as injection site pain or discomfort (2.5%), irritation (1%), and erythema (0.5%). One case of profound bradycardia (26 bpm: BP 100/60 mmHg) was observed in a patient during a 15 minute infusion of 150 mg VIMPAT. This patient was on a beta-blocker. Infusion was discontinued and the patient experienced a rapid recovery.

Comparison of Gender and Race

The overall adverse event rate was similar in male and female patients. Although there were few non-Caucasian patients, no differences in the incidences of adverse events compared to Caucasian patients were observed.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIMPAT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Atroiventricular block, atrial fibrillation, atrial flutter, bradycardia

Immune system disorders: drug hypersensitivity reactions

Psychiatric disorders: Aggression, agitation, insomnia, psychotic disorder

Skin and subcutaneous tissue disorders: Angioedema, rash, urticaria

DRUG INTERACTIONS

Drug-drug interaction studies in healthy subjects showed no pharmacokinetic interactions between VIMPAT and carbamazepine, valproate, digoxin, metformin, omeprazole, or an oral contraceptive containing ethinylestradiol and levonorgestrel. There was no evidence for any relevant drug-drug interaction of VIMPAT with common AEDs in the placebo-controlled clinical trials in patients with partial-onset seizures [see *Clinical Pharmacology (12.3)* in Full Prescribing Information)].

The lack of pharmacokinetic interaction does not rule out the possibility of pharmacodynamic interactions, particularly among drugs that affect the heart conduction system.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Lacosamide produced developmental toxicity (increased embryofetal and perinatal mortality, growth deficit) in rats following administration during pregnancy. Developmental neurotoxicity was observed in rats following administration during a period of postnatal development corresponding to the third trimester of human pregnancy. These effects were observed at doses associated with clinically relevant plasma exposures.