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Review

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Vaccine Information

Beware of distortion by healthy-vaccine effect

New Products

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Too many harms including suicide. Do not use !

Unavoidable Hams of Alzheimer's agent

Translated and modified from MedCheck(in Japanese) Nov. 2023 (N110) and Jan 2024(N111)

In 2007, MedCheck concluded that no drug can be recommended for dementia. It was based on the results from a 4-year randomized controlled trial (RCT) of donepezil which showed that the agent did not help reduce "institutionalization'' as the index of care burden, it increased serious adverse reactions, including death. In France, the reimbursement rate for four Alzheimer's disease agents, including donepezil, was lowered from 65% to 15% in 2011 due to a lack of evidence of long-term therapeutic benefit. However, in Japan in the same year, three drugs other than donepezil were approved. This contrasts with France, where reimbursement for these four agents was finally delisted in 2018.

By using the same methods (CDR-SB) as in the RCT of lecanemab, donepezil improved the score by 0.85 points compared with the placebo group at six months, but was not effective in reducing institutionalization. On the other hand, lecanemab only improved the score by 0.45 points at 1.5 years, even though the RCT was conducted in favour of lecanemab: odds of patients who discontinued due to adverse events was 2.5 times that of the placebo group and those who discontinued were basically excluded from the efficacy evaluation. Institutionalization was not included as a study outcome.

As we conducted further research on lecanemab and the pathogenesis of Alzheimer's disease, the harms of lecanemab are becoming clearer. Lecanemab induces multiple cerebral hemorrhages leading to death and cerebral atrophy, both are closely related with the mechanism of action of lecanemab. We also found that "the amyloid beta theory" claimed as the cause of Alzheimer's disease is not correct (page41 of this issue). It can be inferred that dementia will worsen as brain atrophy progresses.

Major media uncritically report the manufacturer's advertisement claiming that lecanemab, unlike conventional drugs, treats the cause of Alzheimer's disease and delays its progression. Patients are often advised by their doctors that 'if left untreated, the disease will continue to progress' and are encouraged to accept the unreliable treatment. Consequently, truly effective prevention and treatment options, such as aerobic exercise and methods for caring for Alzheimer's patients, such as "Humanitude", will be overlooked.

The burden on the health care economy is also enormous. In Japan, lecanemab has been used since December 25, 2023. The annual cost of the drug is approximately $20,000 for a person weighing 50 kg, and about $30,000 for 60 kg. Although a high-cost compensation system may reduce out-of-pocket expenses, it will still be funded by taxes and insurance, and which could place a burden on the public. In addition, PET examination requires significant out-of-pocket expenses. Do not use lecanemab, even if it were not expensive, as the harm is clear while there is no evidence of efficacy. Please read our series of articles on lecanemab.

Review

Lecanemab removes substitute of lost cells leading to inevitable cerebral hemorrhage and atrophy

Translated and revised from Med Check (in Japanese) Nov. 2023 (N110) and Jan. 2024(N111)

Med Check Editorial Team

Abstract

●Lecanemab is a product of monoclonal antibody that binds to and removes amyloid-β in the brain. It has been found that when used to treat mild cases of Alzheimer's disease, it can cause multiple cerebral hemorrhage leading to death and brain atrophy.

●Cerebral neuronal progenitor cells exposed to mild oxidative stress secrete a moderate amount of amyloid-β which improves cognitive function and stimulates to create new neurons. However, when high concentrations of amyloid-β are produced due to excessive oxidative stress, it interferes with the formation of new nerve cells.

●Hence, the excessive amyloid-β is not the cause of Alzheimer's disease, but is the result of excessive oxidative stress, the real cause of the disease. Even if amyloid-β is reduced, it does not mean that the cause of the disease is removed.

●In the brains of Alzheimer's disease patients, much of the vascular smooth muscle is replaced by amyloid-β. This is the result of damaged smooth muscle cells secreting excessive amyloid-β due to excessive oxidative stress and being replaced by the amyloid-β as substitute.

●When lecanemab removes amyloid-β from blood vessel walls, edema and hemorrhage occur, injuring surrounding brain tissue and subsequently causing brain atrophy. These are common and class adverse effects of monoclonal antibody preparations and are consistent with the mechanisms of pathogenesis of Alzheimer's disease and cerebral amyloid angiopathy and the mechanisms of action of lecanemab.

●It is difficult to imagine that a substance that atrophies the whole brain could improve cognitive function. Nothing about reducing the burden of care is taken into account in the clinical trials. It is not worth paying the high price. Even if it were not expensive, it should not be used because there is no evidence of benefit, but only serious harms.

Conclusions: Reducing amyloid-β, which is not the cause of dementia, will only cause brain atrophy and multiple cerebral hemorrhage, leading to death at the worst. Do not use lecanemab.

Keywords:

amyloid-β, oxidative stress, neuronal progenitor cells, ventricular enlargement, cerebral edema, cerebral hemorrhage, cerebral amyloid angiopathy (CAA), cerebrovascular smooth muscle

Introduction

Lecanemab (Lequenbi®) was launched on December 20, 2023 in Japan. It is indicated for "mild cognitive impairment or mild Alzheimer's disease".

The mechanism of pathogenesis of Alzheimer's disease described in MedCheck in English No. 27 [1] was not sufficient. Subsequent research has revealed greater harms of lecanemab and the mechanisms of pathogenesis of Alzheimer's disease. Serious harms of lecanemab include multiple cerebral hemorrhages leading to death [2], brain atrophy and ventricular

enlargement [3,4]. These are closely related to cerebrovascular amyloidosis (CAA) [5], in which amyloid-β (Aβ) accumulates in the walls of arteries in the brain. Aβ is essential in the mechanism of repairing damage to neuronal cells [6] and vascular smooth muscle cells [7] caused by mild oxidative stress (**Note**). However, excessive oxidative stress impairs the formation of normal neuronal cells and vascular smooth muscle cells that are replaced by the Aβ accumulated. Therefore, we will first explain the mechanisms of pathogenesis of Alzheimer's disease based on new findings. Considering these mechanisms, it may be understandable that lecanemab cannot eliminate the cause of Alzheimer's disease, has no efficacy, and inevitably causes brain atrophy and multiple cerebral hemorrhage, leading to deaths at the worst.

Note : Oxygen is essential for the human body, but reactive oxygen can damage the genes, proteins, and lipids of normal cells in the body, cause cell degeneration and necrosis, and cause aging and various diseases. Nitric oxide (NO), which is released from tissues when reperfusion occurred after prolonged ischemia due to excessive stress or during infection, is a typical reactive oxygen or free radicals. Living organisms have a mechanism to eliminate reactive oxygen, but a state in which reactive oxygen exceeds this ability is called "oxidative stress".

Neuronal progenitor cells secrete Aβ

Even in old age, approximately 700 new neurons are produced in the hippocampus alone per day, or 250,000 new neurons per year [8,9]. When neuronal cells are damaged by oxidative stress associated with prolonged ischemia and re-perfusion, the "neuronal progenitor cells" that are the cells just prior to neuronal cells differentiate into new neuronal cells.

When the DNA of cultured human neuronal progenitor cells was damaged by treatment with hydrogen peroxide (H_2O_2), Aβ40 and Aβ42 that are believed to be the cause of Alzheimer's disease, was secreted [6].

Moderate Aβ creates new nerve cells

A moderate amount of newly secreted Aβ not only enhances cognitive function [1] but also stimulates other living neuronal progenitor cells [10] and neuronal stem cells [11-13] to promote their differentiation and create new neuronal cells.

In other words, when neuronal progenitor cells are damaged by moderate oxidative stress, Aβ is secreted appropriately, stimulating surviving neuronal progenitor cells and neuronal stem cells to recruit new neurons. This mechanism can be described as a feedback function essential for maintaining a healthy brain.

Excessive oxidative stress suppresses neurogenesis

However, excessive oxidative stress injures neurons, damages neuronal progenitor cells severely, and reduces activity of pumping functions by p-glycoprotein in endothelial cells of cerebral blood vessels [1,14-16], Aβ accumulates in the brain to high concentrations [1,14].

In addition, high concentrations of Aβ inhibit the differentiation of neuronal stem cells into neurons [11, 12]. Hence the number of neurons continues to decrease.

Therefore, it can be concluded that the true cause of neuronal cell loss leading to dementia is exclusively excessive oxidative stress, and that Aβ is merely a "result" of excessive oxidative stress. In other words, reducing Aβ does not eliminate the cause of Alzheimer's disease.

Cerebrovascular smooth muscle also secretes Aβ

More importantly, in the arterioles in the brains of Alzheimer's disease patients, Aβ replaces the smooth muscle cells which is essential for blood vessels to constrict and dilate as needed. In some areas, smooth muscle has been completely replaced by Aβ [5].

Cultured cerebral artery smooth muscle cells secreted Aβ40 and Aβ42 when exposed to oxidative stress [7]. Various changes associated with these have also occurred without contradiction. Oxidative stress induced by other methods (iron ions) [17] also resulted in Aβ secretion from vascular smooth muscle cells, and under starvation from vascular endothelial cells [18].

When smooth muscle cells are injured, smooth muscle progenitor cells and smooth muscle stem cells are stimulated and differentiated to produce

new smooth muscle cells [19,20]. Although the data are not as complete as in the case of neuronal stem cells to neuronal cells, it is likely that, similar to neuronal system, moderately secreted Aβ promotes the differentiation of smooth muscle stem cells and creates new smooth muscle cells. However, excessive oxidative stress increases Aβ which is hard to be excreted from the brain, and accumulates excessively, inhibiting the differentiation of smooth muscle stem cells and inhibiting the new generation of smooth muscle cells. If vascular smooth muscle cells are excessively damaged by excessive oxidative stress and new smooth muscle cells cannot be formed, blood vessels will rupture. Hence, Aβ accumulated in arteries is thought to serve as a substitute for smooth muscle to prevent blood vessel from rupturing.

Three cases of death after multiple cerebral hemorrhages

Case 1 [21]: A 65-year-old woman with early stage of cognitive decline but with normal daily activities. Four days after she received three injections of lecanemab during the extension period after the end of the RCT, she developed an ischemic stroke and presented to the emergency room 30 minutes later. After taking computed tomography (CT) just before t-PA (alteplase) administration showed no brain hemorrhage with no contraindication to t-PA. When she received 86% of the planned dose of t-PA, her blood pressure increased to 250/111 mmHg, so the infusion was stopped (increased blood pressure may be due to cerebral bleeding). A CT scan showed extensive, multifocal intraparenchymal hemorrhages. Three days later endotracheal intubation was performed, but she died. The autopsy showed extensive multifocal intraparenchymal hemorrhages, cerebral amyloid angiopathy, "high" Alzheimer's disease neuropathologic changes, and diffuse histiocytic vasculitis with necrotizing vasculopathy involving amyloid deposition within (but not outside) the blood vessel walls.

The reporting physician pointed out "The extensive number and variation in sizes of the cerebral hemorrhages in this patient would be unusual as a complication of t-PA solely related to cerebrovascular amyloid. The findings raise the possibility of cerebral hemorrhages and necrotizing vasculopathy associated with t-PA infusion in a patient with cerebrovascular amyloid who had received lecanemab" [21]. Furthermore, magnetic resonance imaging (MRI) of the head performed 49 days before the use of lecanemab revealed no findings such as microhemorrhage or edema.

The authors of the phase 3 randomised control trial (RCT) of lecanemab counter that there have been reports of fatal large catastrophic intracerebral hemorrhages after t-PA treatment in persons with cerebral amyloid angiopathy (CAA) in the absence of any anti-amyloid medications [22].

Case 2 [23]: A 79-year-old female. After using lecanemab during the extended period, she developed significant cerebral edema, multiple cerebral hemorrhages less than 1 cm in size, and seizures, and died. Several neurologists who reviewed the records noted an association with lecanemab [23].

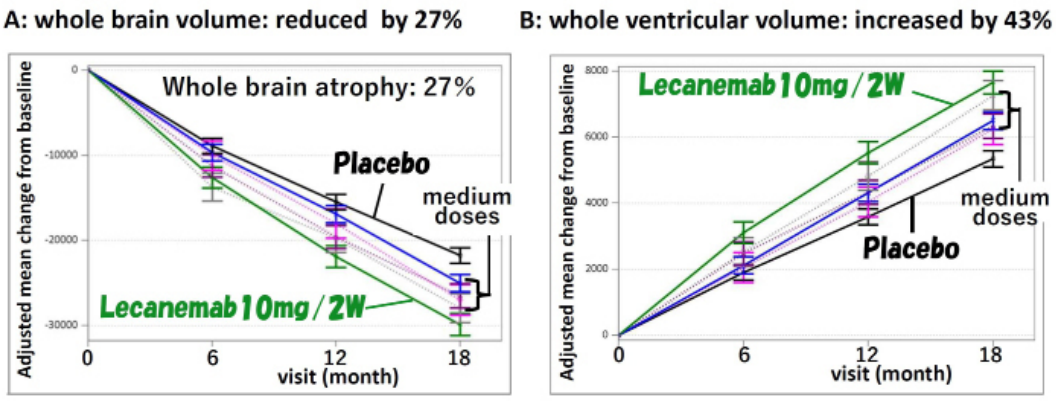
Case 3 [24,25]: An 87-year-old male. During the use of a direct oral anticoagulant (DOAC) apixaban in the extension period, he received lecanemab and fell possibly due to intracerebral hemorrhage. Both (apixaban and lecanemab) were stopped. One month later, he had a myocardial infarction and received another anticoagulant followed by a cerebral hemorrhage leading to death. Eisai does not recognize a causal relationship and claims that the cause was a fall, heart disease, respiratory infection, or recurrence of a mild stroke-like attack [24,25].

In the review report by the Japanese regulatory authorities [26], these three deaths were treated separately from the trial as they occurred after the data collection period of the main trial, and because a relationship with lecanemab could not be ruled out, it was concluded that "a cautionary statement is required on the package insert". However, because it is not treated as an "Boxed Warnings" the alerting effect may be small.

Lecanemab causes brain atrophy: in phase 2

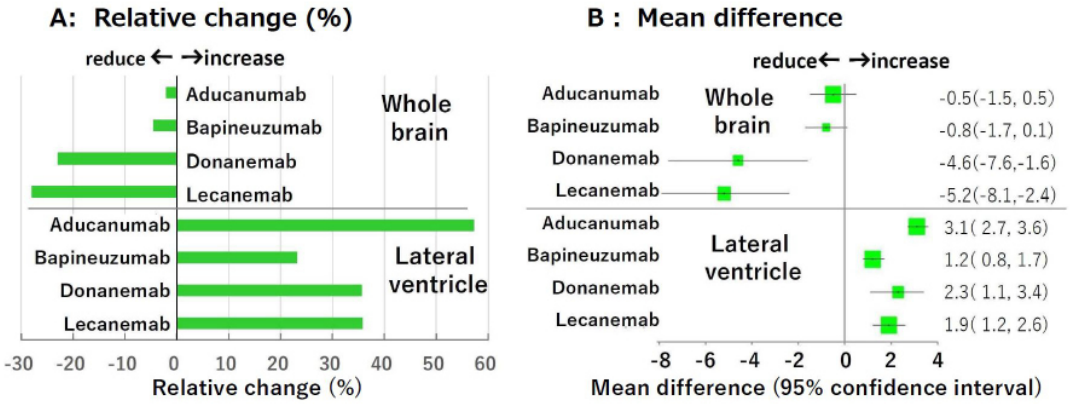
Figure 1 is a graph showing whole brain atrophy (**Fig. 1 A**) and enlarged ventricular volume (**Fig. 1B**) that were

Figure 1: Decreased whole brain volume and increased ventricular volume



The unit is unknown as it is not mentioned in the clinical trial report paper[3].
Figures are cited and modified from ref. [3] Swanson CJ et al. Alzheimers Res Ther. 2021;13(1):80.

Figure 2: Volume change of whole brain and lateral ventricle



Reconstructed from data on ref. [4] Alves F et al. Neurology. 2023;100(20):e2114-e2124.

reported in the Phase 2b clinical trial [3].

Clinical doses of lecanemab resulted in significantly smaller whole brain volume (Fig. 1 A) and enlarged ventricular volume (Fig. 1 B) compared with the placebo group. The figure shows that the whole brain volume decreased 27% more in the clinical dose group than in the placebo group. This means that the degree of brain atrophy was 27% severer than in the placebo group.

On the other hand, the volume of the ventricles, which contains cerebrospinal fluid, was 43% larger than in the placebo group (Fig. 1 B). The enlargement of the ventricles is thought to be due to brain atrophy, and the results are consistent with brain atrophy. Although these results were reported in the phase 2b clinical trial, this point was not reported in the phase 3 trial [27].

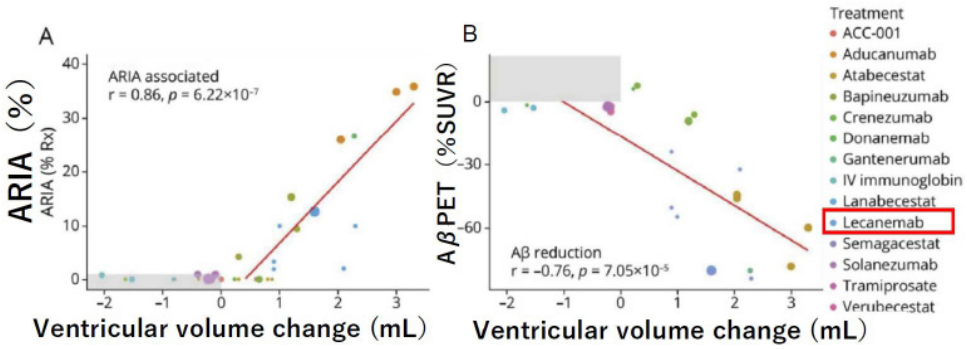
Other monoclonal antibodies also cause brain atrophy

Clinical trials have been conducted on various agents for dementia targeting reduction of Aβ, such as monoclonal antibodies against Aβ and inhibitors of the enzyme secretase, which converts the amyloid precursor protein (APP) into Aβ.

Among them, the results of a meta-analysis of measurements of whole brain volume and ventricular volume were published in April 2023 [4]. Based on the data extracted from the paper, we made Figure 2A to show the relative changes (%) in whole brain volume and ventricular volume due to monoclonal antibodies, such as lecanemab compared with the placebo group. Figure 2B shows mean differences.

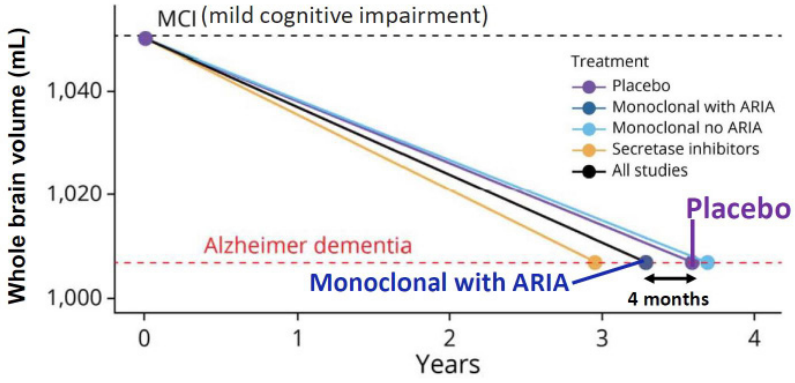
The relative reduction in whole brain volume was greatest with lecanemab at 28%, followed by

Figure 3: Association of volume change with ARIA and amyloid reduction



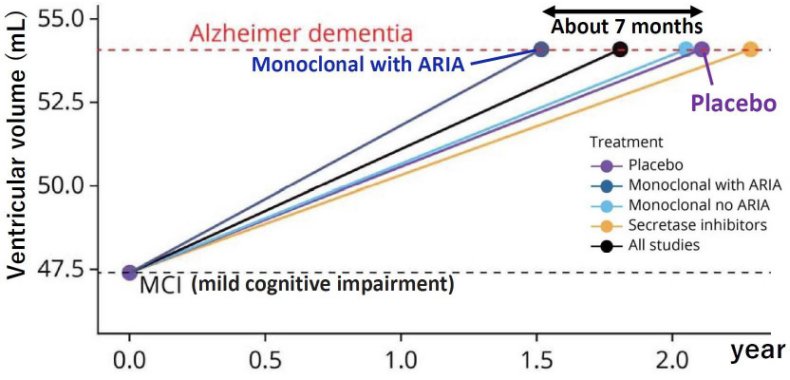
Extracted from Figure 5 on ref. [4] Alves F et al. Neurology. 2023;100(20):e2114-e2124.
ARIA: amyloid related imaging abnormality (brain edema and/or brain hemorrhage)
SUVR：standardized uptake value ratio PET: positron emission tomography

Figure 4: Whole brain volume change from MCI to dementia level



Extracted from Figure 6 on ref. [4] Alves F et al. Neurology. 2023;100(20):e2114-e2124.
ARIA: amyloid related imaging abnormality (brain edema and/or brain hemorrhage)

Figure 5: Ventricular volume change from MCI to dementia level



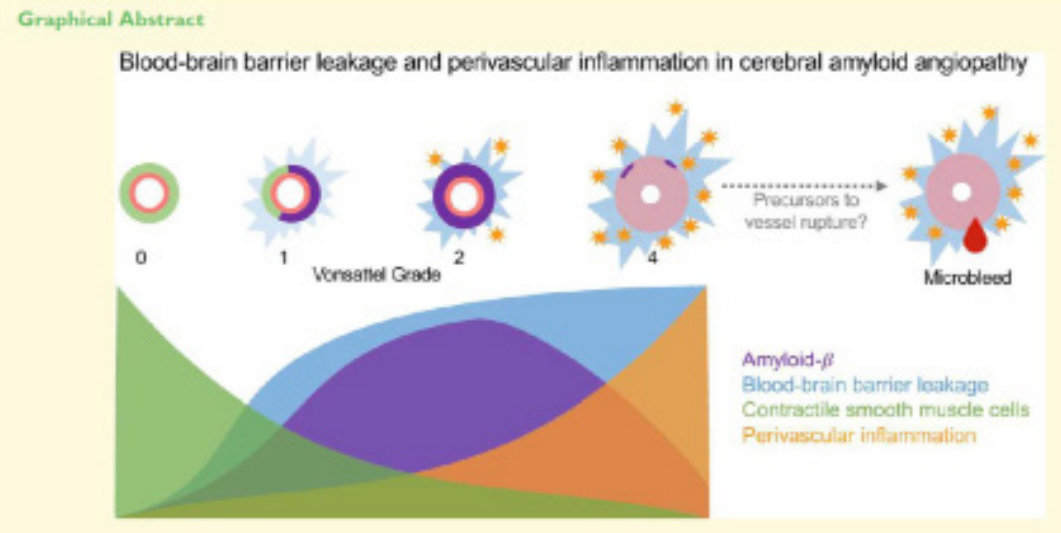
Extracted and modified from Figure 6 on the ref. [4])
It is estimated that it takes 25 months to reach the onset level of Alzheimer's disease, but with monoclonal antibody like lecanemab, this could be shortened to 18 months (by about 7 months).

donanemab. Additionally, aducanumab had the largest increase in lateral ventricular volume at 57%, followed by lecanemab in third place with an increase of approximately 37%.

There was an extremely strong positive correlation (r=0.86, p=6.2×10-7) between the size of this ventricular enlargement and the degree of cerebral edema and cerebral hemorrhage seen on MRI (Figure 3) [4].

It took 3 years and 7 months under the natural course (placebo group) for the degree of brain atrophy to change from non-dementia level to the dementia level. However, with clinical doses of lecanemab and other monoclonal antibody with amyloid-related imaging abnormalities (ARIA: brain edema and hemorrhage), it took 3 years 3 months or 4 months earlier (9.3%) than the natural course (Figure 4) [4]. By analysing the ventricular volume change from mild cognitive impairment (MCI) to dementia level, it is shortened from 25 months to 18 months by 7 months (28%) (Figure 5).

Figure 6: Illustrated Progression of cerebral amyloid angiopathy



Cited from the graphical abstract on the ref. [5] Kozberg MG et al. Brain Commun. 2022 Sep 26;4(5):fcac245.

Brain atrophy after edema and hemorrhage

In Alzheimer's disease brains, neuronal progenitor cells are destroyed by oxidative stress and excitotoxicity, and neurons cannot be replenished. In addition, the smooth muscle cells in the arterial wall are damaged in many places, so they are replaced and reinforced by Aβ.

As the disease progresses further, Aβ also disappears, causing fibrinoid necrosis, and the vessel wall becomes extremely fragile (**Figure 6**) [5].

Monoclonal antibodies bind not only to soluble Aβ but also can bind to and remove insoluble Aβ. They combine to form immune complexes, and as they are removed by the immune response, inflammation occurs leading to edema. Also, if a small amount is removed from the blood vessel wall and a small defect is created, blood components will leak out and edema will occur. If a large amount of Aβ is suddenly removed, defects in the blood vessel wall will cause bleeding and injure the surrounding brain tissue. After hemorrhagic injuries have healed, the brain will shrink and the ventricles will enlarge.

It is like replacing a glass door that has been broken in a rainstorm with a plastic thin sheet to protect it from the rain and wind, but then peeling off the plastic blaming the plastic as the cause of glass broken.

The manufacturer blames other illnesses for the patient's death due to multiple cerebral hemorrhages after using lecanemab [26]. It is like saying the house was flooded during a rainstorm because it was very old but not because of the removal of the plastic. A reanalysis of the results of the phase 3 trial reported that quality of life (QOL) has improved [28], but this is also unreliable as the results of those who dropped out of the trial are not considered.

In Practice: Do not use lecanemab

Cognitive function in people who were unable to continue the study due to brain edema or hemorrhage have not been properly examined, so the efficacy on change of cognitive function cannot be trusted. Moreover, lecanemab induce brain atrophy definitely, and may induce multiple cerebral hemorrhages leading to death at the worst. Therefore, lecanemab may progress Alzheimer's disease rather than delay it. The use of lecanemab is extremely dangerous. Do not use it even if it were not expensive.

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Is it true: "Several vaccines reduce Alzheimer's disease"?

Beware of distortion by healthy-vaccine effect

Translated and revised from Med Check(in Japanese) Nov. 2023 ; 23 (110) : 135-137

Med Check Editorial Team

Abstract

- There are several articles titled "Several vaccines associated with reduced risk of Alzheimer's disease". MedCheck editorial team examined the original articles to investigate if it really could be considered vaccine effects.
- The original paper was an observational study based on hypothesis that Alzheimer's disease may be prevented by reducing infection with neuroinflammation as one of the causes of Alzheimer's disease. However, this hypothesis itself was not reasonable, because the assumed number of vaccine-preventable Alzheimer's disease patients determined by the Number needed to treat exceed the maximum number of preventable infectious diseases by each vaccine.
- The observational studies claiming a reduction in other diseases that vaccines did not originally target almost always neglect healthy-vaccinee effect: vaccinated persons have better health status than unvaccinated persons.

Conclusions: Observational studies that claim vaccine effectiveness or safety need to be read critically with attention to distortion by healthy-vaccinee effect.

Keywords: tetanus, diphtheria, pertussis, shingles, pneumococcus

Introduction

Med Check Editorial Team emphasized the need to be aware of healthy-vaccinee effect when interpreting studies investigating vaccine efficacy or adverse reactions [1]. Some news reports have been published on the possibility that "certain vaccinations may reduce risk of Alzheimer's disease [2-4]" since August 2023. However, after studying the original article, these news reports needed to be read critically.

What does the original paper claim?

The original article was based on the hypothesis that "various infections induce neuroinflammation, which in turn causes Alzheimer's disease, and that suppressing infections with vaccines would reduce Alzheimer's disease, or that vaccines activate the immune system, which in turn would reduce Alzheimer's disease". The study was an observational study that followed approximately 1.65 million people aged 65 years or older in the USA for 8 years and compared the incidence of Alzheimer's disease with and without previous vaccination with tetanus, diphtheria, pertussis, herpes zoster and pneumococcal vaccines [5]. The authors of the paper performed propensity score matching (**Note 1**) and reported that the incidence of Alzheimer's disease was approximately 30% lower in the vaccinated group compared with the unvaccinated group **(Appendix 1)** .

Note 1: Propensity score matching is a method to adjust for baseline characteristics which could affect outcome. For tetanus, diphtheria and pertussis vaccines, analyses have been conducted with approximately 120, 000 people in the vaccinated group and 1.53 million people in the unvaccinated group, adjusted for age, sex, race, smoking history and prevalence of hypertension, diabetes, asthma, atrial fibrillation, congestive heart failure patients, etc.

Table: Maximum number of vaccine-preventable infection case (U.S. age ≧ 65)

	Vaccinated population*a	Unvaccinated population*a	Infected persons*b	Maximum number of vaccine-preventable infectious disease cases*c	Number of vaccine-preventable AD patients assumed by calculation using NNT*a
Infection	A	B	C	D(=A × C/B)	E
Total of diphtheria, pertussis, tetanus	23,841,674	16,636,550	4,147	**5,943**	714,226
Shingles	15,988,898	24,489,326	3,238,258	**2,114,235**	427,047
Pneumococcus	27,929,975	12,548,249	81,949	**182,402**	856,576

*a: Details were shown in Appendix 1. on this slides

*b: Details were shown in Appendix 2. on this slides

*c: To simplify the calculation, vaccine efficacy is assumed to be 100% (Assuming that "vaccinated persons are not infected".)

If infectious diseases cause Alzheimer's disease (AD), the upper limit of "vaccine-preventable AD patients" is maximum number of vaccine-preventable infectious disease (column D).

However, for diphtheria, pertussis, tetanus, and pneumococcus, "Number of vaccine-preventable AD patients assumed by calculation using NNT (column E)" is much larger than "maximum number of vaccine-preventable infectious disease cases (column D)".

Therefore, it is not reasonable to claim that vaccines can prevent Alzheimer's disease based on the hypothesis "Alzheimer's disease is prevented by reducing infection with neuroinflammation as one of the causes of Alzheimer's disease".

The number of vaccine-preventable Alzheimer's patients outweighs the number of vaccine-preventable infected patients!?

Suppose the hypothesis that "vaccines prevent each infection and prevent Alzheimer's disease following those infections" is correct, based on the Number needed to treat: NNT (**Note 2**) described in the paper, the number of people aged 65 years and older in the US (about 40 million) [6], and the vaccination rate for each vaccine vaccination rates [7], the following calculations can be made. Over the eight-year period from September 2011 to August 2019, the tetanus, diphtheria and pertussis vaccines should have prevented about 720,000 people from Alzheimer's disease, the shingles vaccine about 430,000 people, and the pneumococcal vaccine about 820, 000 people (**Appendix 2**).

On the other hand, according to US infectious disease statistics [8-12], it could be calculated that in the eight-year period from September 2011 to August 2019, approximately 4,100 Americans aged 65 years and older overall had either tetanus, diphtheria, pertussis, 3.28 million had shingles and approximately 82,000 had pneumococcus (details were shown in **Appendix 3**)

If so, the calculation is that for tetanus, diphtheria, pertussis and pneumococcal infections, the number of cases of (supposedly) vaccine-preventable Alzheimer's disease is much higher than the number of vaccine-preventable infections (**Table**).

Note 2: NNT is indicator of how many people need to be vaccinated to prevent one target disease, i.e., if NNT = 33, thirty-three people need to be vaccinated to prevent one person from contracting the target disease.

Any vaccine is 30% effective in reducing Alzheimer's disease!?

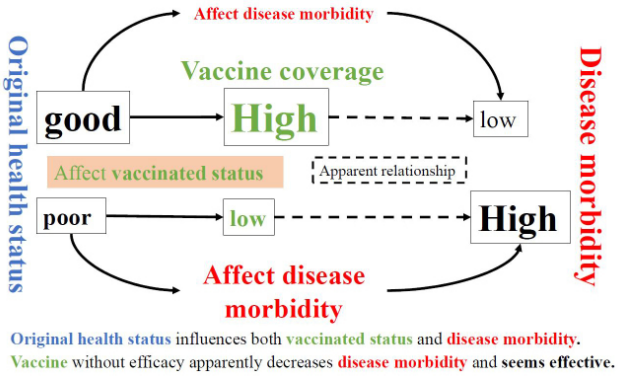
It is strange that any vaccine is effective in reducing Alzheimer disease by 25 to 30 % and the NNT is in the 30 to 40 range (**Appendix 1**) [5]. If these vaccines reduced infection rates and subsequent Alzheimer's disease, there should be over order of magnitude difference in NNT for each vaccine type. Because the estimated incidence of shingles is approximately 800 times higher than diphtheria, pertussis and tetanus combined, and approximately 40 times higher than pneumococcus.

The discussion in the paper [5] argues that the reduction in infection rates and activation of the immune system by the vaccine may have contributed to the reduction in Alzheimer's disease, but the claim that "the reduction in infection rates reduced subsequent Alzheimer's disease" is not appropriate.

Propensity score matching is not perfect for adjusting bias

Jackson et al. have published a study comparing all-cause mortality risk between the influenza vaccinated

Figure：How healthy-vaccinee effect distort the vaccine study



and the non-vaccinated [13]. They showed that the total mortality risk was lower in vaccinated persons not only in the influenza epidemic season but also in the pre-epidemic season. This was due to healthy-vaccinee effect (bias), which could not be adjusted by propensity score matching [13].

In the original paper [5], the differences in proportions, such as diabetes and atrial fibrillation sufferers, have been adjusted, but not for the severity of these diseases. For example, patients with moderate or severe disease are considered ineligible for vaccination [14-16], and these individuals may also have originally an increased risk of Alzheimer's disease [17,18].

Conclusion:

Beware of distortion by healthy-vaccine effect

Although there was an observational study showing that BCG vaccination was associated with a reduction in COVID-19 infections (about 40%) [19], a later published paper on a randomised controlled trial showed that BCG vaccination does not reduce COVID-19 infections [20]. Another paper stated that the results of a seemingly 30% reduction in COVID-19 hospital admissions and deaths due to influenza vaccination was in fact because of health-vaccine effect [21].

There are several other observational studies in which diseases that vaccines are not supposed to prevent appear to be reduced in the vaccinated group [22-24]. However, when reading these papers, it is important to have a critical eye and take into account the impact of distortion by healthy-vaccinee effect (**Figure**).

Appendix 1: Reported proportion of petients with Alzheimer's disease among vaccinated and unvaccinated, and NNT

Vaccine	Vaccinated			Unvaccinated			RR	RRR (VE)	ARR	NNT
	N	AD	(%)	N	AD	(%)				
Tdap/Td vaccine	116,400	8,370	7.19	116,400	11,857	10.19	0.71	29.4	0.030	**33**
HZ vaccine	198,847	16,106	8.10	198,847	21,417	10.77	0.75	24.8	0.027	**37**
Pneumococcal vaccine	260,037	20,583	7.92	260,037	28,558	10.98	0.72	27.9	0.031	**33**

Compiled from paper Table 2 in Harris et al. [5] J Alzheimers Dis 2023;95(2):703-18

Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; **Td:** tetanus toxoid and reduced diphtheria toxoid, **HZ:** herpes zoster, **N:** number of propensity score matched population, **AD:** Alzheimer's disease, **RR:** relative risk, **RRR:** relative risk reduction, **VE:** vaccine effectiveness, **ARR:** absolute risk reduction, **NNT:** number needed to treat.

Appendix 2: Number of vaccinated and Alzheimer's disease to be reduced by each vaccine (U.S. ≧ 65)

	Population in 2010*a	Vaccine coverage*b	Vaccinated population	NNT	Number of vaccine-preventable AD patients assumed by calculation using NNT
Infection	A	B	C(=A × B)	D	E(=C/D)
Total of diphtheria, pertussis, tetanus	40,478,224	58.9%	23,841,674	33	**714,226**
Shingles	40,478,224	39.5%	15,988,898	37	**427,047**
Pneumococcus	40,478,224	69.0%	27,929,975	33	**856,576**

*a: https://www2.census.gov/programs-surveys/popest/tables/2010-2019/national/asrh/

*b: https://www.cdc.gov/mmwr/volumes/70/ss/ss7003a1.htm

AD: Alzheimer's disease

If "vaccines reduce the number of infected persons and thereby prevents Alzheimer's disease (AD)", then "the number of AD patients that would be reduced by the vaccine" will always be less than the number of persons suffering from infectious diseases. This is because the assumption is made that this AD develops from infected patients (Below).

Appendix 3: Estimated number of infectious disease patients in the U.S. aged 65 years and older from 2011 to 2019 (8 years).

Infection	Diphtheria from 1996 to 2018 (23 years, all-age groups)*a	Pertussis from 2000 to 2016 (17 years)*b	Tetanus from 2009 to 2017 (9 years)*c	Incidence*d-f (/100,000 person-years)	Population over 65 years old (2010s)*f	Estimated infected persons (8 years)
Diphtheria	14					5
Pertussis		8,177				4,089
Tetanus			60			53
Total of diphtheria, pertussis, tetanus						**4,147**
Shingles				1,000	40,478,224	**3,238,258**
Pneumococcus				25	40,478,224	**81,949**

*a: https://www.cdc.gov/vaccines/pubs/pinkbook/dip.html
*b: https://academic.oup.com/cid/article/68/10/1634/5087840
*c: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt16-tetanus.html
*d: https://www.cdc.gov/shingles/surveillance.html
*e: https://www.cdc.gov/pneumococcal/surveillance.html
*f: https://www2.census.gov/programs-surveys/popest/tables/2010-2019/national/asrh/

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GLP-1 agonist for obesity: Semaglutide (Wegovy®)

Too many harms including suicide. Do not use ！

Translated and revised from Med Check (in Japanese) Sep 2023; 23 (109)：108-111

Med Check Editorial Team

Abstract

- Semaglutide is one of the glucagon-like peptide-1 (GLP-1) agonists already marketed for type 2 diabetes (Ozempic® subcutaneous injection, Reversus® tablets). In March 2023, the same ingredient was approved for the treatment of "obesity" as Wegovy® subcutaneous injection. It will be launched in Japan in February 2024. The maintenance dose of Wegovy® (2.4 mg once weekly) is approximately five times the standard maintenance dose for diabetes (0.5 mg once weekly).
- The purpose of obesity treatment is to improve patients' health and extend their life expectancy by reducing weight of severely obese individuals.
- Semaglutide reduces weight by decreasing appetite. However, this is the result of the action of semaglutide on the brain to stimulate the nerves, causing a high incidence of gastrointestinal problems, such as severe nausea, vomiting, and/or diarrhea. It also affects health by increasing pancreatitis, gallstones, cholecystitis, retinopathy, and other harms contrary to the original purpose of this treatment. Carcinogenicity is also a common adverse effect of GLP-1 agonists observed in animal studies.
- Significant increase in suicidal ideation associated with liraglutide, another GLP-1 agonist for obesity, was found. European Medicines Agency (EMA) is investigating the causality with GLP-1 agonists, including semaglutide.
- The basic weight control methods for severe obesity consists of thorough program for diet and exercise. The indication for Wegovy is strictly defined by the package insert, but even if it were indicated it should not be used.

Conclusion: **Do not use semaglutide (Wegovy®) even if the indication criteria were met.**

Keywords:
obesity, weight loss, nausea, vomiting, carcinogenicity, cosmetic and slimming, suicidal ideation

Slightly overweight people live longest

There are many studies with millions of people by life insurance companies that have examined the relationship between obesity index and life expectancy [1-3]. In all studies, people with a body mass index (BMI) of about 25 kg/m2 (units omitted below) have the lowest risk of death, and the risk is not much higher in people with a BMI up to 28 [1-5]. The same is true for people with diabetes and hypertension. Moreover, among Japanese people with diabetes, those with a BMI of 31 or higher had no difference in life expectancy compared with those with a BMI of 26 to 28. Obesity which could shorten life expectancy may be 35 to 40 of BMI or higher in the United States. It may be true also in Japan.

Therefore, it can be said that people who are overweight (BMI=25 to 30) are healthier or have similar risk as those who have a BMI of 22, the so-called standard weight, and are not eligible for treatment at all [4, 5].

There are no studies showing that weight reduction, especially drug-induced weight reduction, increases life expectancy.

Med Check's Evaluation: Unnecessary and harmful

Generic Name: Semaglutide

Product Name: Wegovy® Subcutaneous Injection

Indications: Obesity, but it is limited to cases with hypertension or dyslipidemia or type 2 diabetes mellitus in which diet and exercise therapy do not provide adequate relief and in which the following conditions are met:

- BMI of 27 kg/m^2 or higher and two or more obesity-related health problems
- BMI of 35 kg/m^2 or higher with at least one of the above problems

Dosage and administration: Usually initial dosage of semaglutide for adults is 0.25 mg of subcutaneous injection once weekly. Thereafter, the dose should be increased at 4-week intervals in the order of 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg once weekly by subcutaneous injection. 2.4 mg is the maintenance dose.

Price: It will be launched in February 2024. But drug price not yet listed

Manufactured and distributed by: Novo Nordisk Pharma

Japan's guideline for obesity is disease mongering

However, the 2022 guidelines of the Japan Society for the Study of Obesity [6] define obesity as a BMI of 25 or higher, and among the people whose BMI is 25 or higher, those who have at least one of the 11 diseases or health problems, including hypertension, dyslipidemia, diabetes or coronary diseases, are diagnosed as "obesity syndrome" and are subject to treatment for weight reduction.

The basis for this is the studies which examined only the relationship with the development of hypertension and diabetes, and none of them examined the relationship with mortality, especially total mortality. Severely obese people (BMI 35 or higher: 90 kg or more for a height of 160 cm and 102 kg or more for a height of 170 cm), for whom weight loss could potentially increase life expectancy, account for only 0.9% of the adult population in Japan.

Treatment of Obesity

The Japan Society for the Study of Obesity also states that the goal of obesity treatment is to "prevent or improve health problems through weight reduction" and that "weight reduction defeats the purpose if it leads to health impairment".

It also states that the basis of weight reduction treatment is diet and exercise, which is appropriate in itself. It also mentions about the effectiveness of a life diary and a weight diary with graph after achieving weight reduction goals through diet and exercise, and the practice of the chewing method [6]. However, it ignores "life expectancy", which is the most important goal of healthcare.

The problem with the Society's guidelines is that the goal of pharmacotherapy is the prevention of cardiovascular disease (cardiovascular death and combined incidence of myocardial infarction and stroke), and all-cause mortality is not considered [7].

The inappropriate use of glucagon-like peptide-1 (GLP-1) agonists in non-obese people has been rampant since several years ago under the name of GLP-1 diet [8], and national consumer affairs centers nationwide have been receiving an increasing number of consultations regarding clinics offering cosmetic medicines online since around 2017 [9]. Moreover, the Japan Medical Association [10] and Japan Diabetes Society [11] and pharmaceutical companies [12] have successively issued warnings against the off-label use of the drugs for slimming and cosmetic purposes.

Let us now take a closer look at Wegovy® subcutaneous injection.

Weight reduction effect by Wegovy®

The initial dose of semaglutide formulation (see Box for summary) is 0.25 mg subcutaneously once weekly. The dose is titrated up every 4 weeks, and the maintenance dose is 2.4 mg once weekly. This maintenance dose is 4.8 times the usual maintenance dose (0.5 mg/week) for type 2 diabetes.

If the patient loses appetite and weight with the drug, it is considered a harm of the drug. "The effect of Wegovy (=weight reduction)" takes advantage of this harmful effect. The appetite-lowering and weight-loss effects of GLP-1 agonists are primarily the results of their action on GLP-1 receptors in the brain to reduce appetite and slow gastrointestinal motility

(delayed release) to cause indigestion, as mentioned by the manufacturer [13] and regulatory authorities [14]. The tolerance is built for delayed emptying of gastric contents after a short period of time, but the central effect is maintained for a long time [15].

The weight reduction effect was obvious. After 68 weeks, the placebo group lost weight by 2-3%, but the Wegovy 2.4 mg group lost weight by 10-15%. In the largest study, the Wegovy 2.4 mg group lost weight by 15.6%.

Faster pulse, increased heart disease and death

Adrenergic-mediated action is essential for weight loss with GLP-1 agonists, because GLP-1 did not decrease body weight of triple beta-adrenoreceptor knockout mice [16]. When GLP-1 receptors in the sinus node, which regulates heart rhythm, are stimulated, β1 adrenaline acts to accelerate the pulse rates [17]. Thus, the weight-loss effects of GLP-1 agonists and their β-adrenergic stimulation are inseparable, and long-term use of GLP-1 agonists may increase cardiovascular disease and psychiatric disorders.

A meta-analysis of clinical trials of GLP-1 agonists in diabetes reported a reduction in cardiovascular disease [18, 19]. However, in clinical trials, the frequency of nausea and vomiting was extremely high in the GLP-1 agonist group, and it was easy to determine whether the assigned substance was GLP-1 agonist or placebo. This can break double blinding shortly after the start of the trial, making it susceptible to data manipulation [15].

In addition, pulse rate is faster in clinical trials of Wegovy [13, 14], as well as in trials of other GLP-1 agonists. Long-term use of drugs that increase the pulse rate worsens heart diseases, which contradicts the results of meta-analysis which showed a reduction in cardiovascular disease.

In fact, a trial comparing the GLP-1 agonist liraglutide to placebo in heart failure patients, 60% of whom had diabetes complications, showed a significant 34% increase in death + cardiovascular readmission + emergency department visits at 6 months [20, 21].

Too many harms

Because GLP-1 receptors are expressing on cells throughout the body, including the heart, brain, gastrointestinal tract, pancreas, blood vessels, kidneys, and immune system [16], GLP-1 agonists can cause symptoms and adverse reactions in various organs.

Gastrointestinal disorders: Nausea, vomiting, diarrhea, constipation, belching, abdominal pain, and gastroesophageal reflux disease, are particularly common. Serious adverse events include cholecystitis, cholelithiasis, acute pancreatitis, atrial fibrillation, atrial tachycardia, acute myocardial infarction, bile duct stones, ureteral stones, pyelonephritis, vertigo, ketoacidosis, and diabetic retinopathies [13, 14].

Carcinogenicity: In a carcinogenicity animal study of semaglutide [22], the lowest dose of semaglutide increased thyroid C-cell tumors (including benign tumors) in both mice and rats. In particular, thyroid C-cell adenocarcinoma was increased in rats with Wegovy at one-eighth the dose used in humans. A significant increase in cancer was also observed in clinical trials of GLP-1 agonists [15], and biliary adenocarcinoma and renal clear cell carcinoma were also seen in clinical trials of Wegovy. The most recent systematic review revealed that GLP-1 agonist treatment was associated with a significant increase in the risk of overall thyroid cancer and odds ratio was 1.76 [95% CI 1.00, 3.12] (P = 0.05) by meta-analysing studies with two years or more [23].

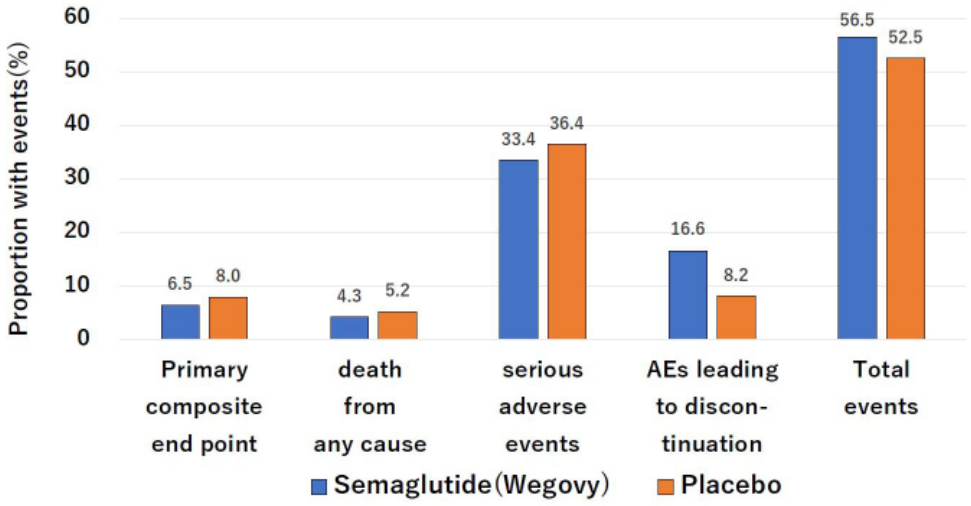
Psychiatric effects including completed suicide

Suicidal ideation and self-harm have been reported in Iceland and the EMA has initiated a review [24]. In a review of clinical trials of liraglutide [25], the incidence of suicidal behavior showed non-significant increase in the liraglutide group: 0.3% (9/3384) versus 0.1% (2/1941) in the placebo group (P = 0.208).

However, in the supplementary appendix of the report [25], it is revealed that the number of events in the liraglutide group was eleven.

Kelly et al. [26] reported three suicidal cases (one completed and two attempted suicide) among 125 liraglutide treated adolescents while no suicidal event was reported in the placebo group. The meta-analysis of both reports yielded a pooled odds ratio (OR) by conditional maximum likelihood as 4.57

Figure : Outcome, adverse and overall events from SELECT trial



Primary composite outcome events, death from any cause and serious adverse events were less reported in the Wegovy group but adverse events leading to permanent discontinuation of trial product, irrespective of seriousness were far more reported in Wegovy group than in Placebo group. Overall events were more reported in Wegovy group: Odds ratio was 1.17 (95%CI: 1.13, 1.22) (p<0.0001). Because participants with permanent discontinuation of trial product were censored at the point of discontinuation, those who had primary composite outcome events might not have been counted as having event. The reported results are extremely distorted by the unbalanced proportion of those with permanent discontinuation of trial product. Moreover, they have not report about suicidal events that FDA's documents pointed out.

(exact Fisher 95%CI: 1.04, 41.71) (p=0.036, I^2 =0%).

In the documents reviewing Wegovy by the Food and Drug Administration (FDA) [27] the followings were reported: "5 suicidal ideation among 2650 participants in semaglutide 2.4mg group, while 2 among 1529 participants with placebo group were reported." Meta-analysis of 3 data above yield pooled odds ratio 2.98 (95%CI: 0.98, 12.11)(p=0.05, I^2=0%).

Moreover, in the same document [27] it was reported that "Blinded data: Blinded data as reported in the NDA and 120-day safety update identified 4 subjects in the SELECT CVOT with fatal events of suicide (1 suicide attempt and 3 completed suicides that were listed as fatal events). As the events are blinded, an assessment of suicide with semaglutide cannot be completed at this time."

SELECT trial reported nothing about suicidal events

Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial tested the hypothesis that the addition of semaglutide to standard care would be superior to placebo in reducing the risk of major adverse cardiovascular events among patients 45 years or more of age with overweight or obesity and preexisting cardiovascular disease who did not have diabetes [28].

Primary cardiovascular efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-first-event analysis.

As shown in the **Figure**, the primary composite outcome events, death from any cause and serious adverse events were less reported in the Wegovy group, while adverse events leading to permanent discontinuation of trial product, irrespective of seriousness (odds ratio was 2.24) were far more reported in Wegovy group than in Placebo group. Overall unwanted events (sum of these events) were more reported in Wegovy group: Odds ratio was 1.17 (95%CI: 1.13, 1.22) (p<0.0001).

It is assumed that the participants with permanent discontinuation of trial product were censored at the point of discontinuation. If it is correct, those who had primary composite outcome events might not have been counted as having events. The reported results would have been extremely distorted by the unbalanced proportion of those with permanent discontinuation of trial product.

Moreover, **they have not reported about suicidal events that FDA's documents [27] pointed out.**

SELECT results may be distorted by blinding failure

Hazards (or odds) of events varied by the period after the start of the study. For example, Figure 1B of the SELECT trial [28] is the time-to-first-event analysis for death from cardiovascular cause. Odds ratio (95%CI) of cardiovascular death within every 6 months after the start of the trial extremely fluctuate: 0.44 (0.24, 0.83) during the first 6 months to as high as 2.08 (1.25, 3.46) during 18 to 24 months and as low as 0.24 (0.12, 0.49) during 36 to 42 months.

As Wegovy induced frequent gastrointestinal adverse reactions, allocation was very easy to be speculated and the blinding may be easily broken. Very high odds ratio (2.24) for the adverse events leading to permanent discontinuation of trial product and the fluctuating odds ratios may be the results of blinding failure (details will be discussed in the next issue).

Obese people have less suicidal ideation

As a reason for increased risk of suicidal ideation, it is sometimes claimed that severely obese individuals have a pre-existing mental illness, which increases their risk of suicidal ideation. However, this is incorrect. A follow-up survey of approximately 14,000 men and women between the ages of 18 and 26 in the United States [29] revealed the opposite results. Among women of any BMI group, there was almost no difference. For men, compared with the reference BMI (18.5-24.9), odds ratio of overweight people (BMI 25-29.9) was significantly lower at 0.62, and even those who are fully obese (BMI 30 or higher) it was 0.5 to 0.75. Severely obese people with BMI of 40 or above did not tend to have more suicidal ideation: OR was only 0.5 [29].

Retinopathy should not be overlooked

Wegovy, as a hypoglycemic agent, reduces elevation of blood glucose levels, but increases retinopathy [13]. By combining the data from three randomized contolled trials (RCTs) comparing placebo, low dose, and clinical dose (2.4 mg) of Wegovy, annual incidence of retinopathy (persons/100 person-years) was 3.5 in the placebo group, 5.5 in the low dose group, and 6.7 in the clinical dose group. Retinopathy increased with increasing dose (dose-response relationship, p = 0.0012) [13].

In a study of semaglutide for diabetes [30], the risk of developing retinopathy was also significantly increased, 1.76 times that of the placebo group, and all-cause mortality was slightly higher in the semaglutide group than in the placebo group (hazard ratio 1.05).

Continuous unnatural stimulation

Physiological GLP-1 in the body plays an important role by working in tissues throughout the body, but its effects are short-lived and only activated when necessary. The half-life of physiological GLP-1 is 1-2 minutes, meaning it is completely eliminated within in 5 to 10 minutes if not needed. However, a GLP-1 agonist, such as Wegovy® , which requires only once-weekly injection, continuously stimulates various parts of the body even when GLP-1 is unnecessary.

Physiological GLP-1 also stimulates the receptor vascular endothelial growth factor (VEGF), which increases vascular endothelial cells and proliferates blood vessels [31,32], but does not work when not needed. However, if a GLP-1 agonists are continuously used when it is unnecessary, it may cause blood vessels to proliferate, causing or worsening retinopathy. Sustained stimulation of VEGF has also been found to increase cancer [32].

These explain why there are so many unfavorable effects.

In practice

Semaglutide may reduce weight, but it is not a healthy way to lose weight. The basic principle of weight reduction treatment for obesity is to stick with a thorough regimen of diet and exercise with behavioral therapy.

Wegovy should not be used, even if it meets strict indication criteria. Nor should it be used for weight loss of non-obese people.

Appendix:
Importance of Behavioral Therapy and Support

Diet and exercise are the mainstays of weight reduction treatment. However, for individuals with severe obesity which requires treatment, patiently sticking with diet and exercise might be challenging. Behavioral therapy is important in changing the behavior itself, including eating behavior.

In a behavioral approach, as a method of self-management, patients and medical professionals examine together what has been achieved and what should be improved based on the recording of usual food intake and physical activity at each visit or nutritional counseling. (The recording is essential because the examination is based on objective data on actual food intake and physical activity.) Then the patients take home the homework and practice it. The basic approach is that medical professionals assist the patients in a way that maintains their motivation to lose weight and encourages them to move to the next step. It is also important that their family and friends support them so that they can stay motivated.

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