The new Alzheimer's Disease treatments – very interesting but not yet ready for "Prime Time"

Alzheimer's disease is considered a slowly progressive neurodegenerative disorder with an average life expectancy of 8 to 10 years, ranging up to 25 years. Up to now, we have only had access to symptomatic treatments such as cholinesterase inhibitors (eg donepezil) or memantine. Recently new drugs have been developed to treat Alzheimer's disease that do look very exciting.

There have been three monoclonal antibodies that have been publicised for the treatment of early Alzheimer's disease. These medications remove the various forms of the protein amyloid, from the brain. The first medication to be developed that had statistical benefit was Aducanumab. The trials looking at Aducanumab were initially considered to be negative trials. On subgroup analysis this medication was found to possibly show a 22% slowing of disease. This was controversial at the time as the impression was this change did not provide a clinically significant result, especially with regards to the risks associated with this medication. Despite opposition, the FDA approved Aducanumab. The two other medications are Lecanemab and Donanemab.

All three medications have had a statistically positive results in the phase III treatment trials, but there still remains doubt over the clinical significance of the trials (ie you can see a small change on assessment score, but does this mean that the medication makes a clinical difference – ie makes a clear difference to someone's function and life)

To assess the effect of these medications, rating scales are used. The common rating scale for all 3 medications is the CDR-SB (Clinical Dementia Rating Scale). This scale is out of 18. The Lancet Editorial 2022 referenced a 2019 study that suggested that a "Minimal clinically important difference for the CDR in MCI was a 0.98 change on the 18-point scale and a 1.63 point change in the 18 point scale for Alzheimer's disease".

Aducanumab - 4 week infusion over 19 months

Aducanumab Emerge only ½ of the patient in emerge and engage completed the study (1812 out of 3285)	CDR (clinical dementia rating scale, out of 18)	RBANS (measure of memory)	ARIA – brain haemorrhage and swelling related to the drug	Death
High dose	2.51	60.7	41.7	11 (3+8)
Placebo	2.47	60.5	10.2	5
Absolute difference	**0.39** (22% slowing in decline)	0.2		

Lecanemab -2 weekly infusion for 18 months

Lecanemab 1795 people	CDR	Non progressors by 1 point on CDR	ARIA -E	ARIA- H	ARIA	Death – total of 13 in trial
lecanemab	1.27/18	24%	12.6%	17.3%	21.5	3 in extension of trial
Placebo	1.66/18	32%	1.7%	9.0%	9%	0 in extension of trial
Absolute difference	**0.45** (27% slowing in decline)	8%				

Donanemab - 4 weekly infusion for 12 to 18 months

Donanemab 1736 people 76% completed the trial	CDR – 18 point scale	iADRS - 144 point scale	Slowing of progression	ARIA -E	ARIA- H	ARIA total	Death
Donanemab	1.20	-6.02	47%	24.0%	31.4	36.8	3
Placebo	1.88	-9.27	29%	2%	13.6%	14.9%	1
Absolute difference	**0.67** (29% slowing in decline)	3.25/144 (22% slowing)	18%				

All these medications can be associated with infusion related events – anaphylaxis.

To put things into perspective – Donanemab had the biggest effect on CDR and this is thought to translate into a 4-7.5month slowing of a disease that in itself, can last decades. None of these medications reverses or repairs brain damage already caused by the disease. A lot of the expert commentary notes that they could be considered a first step in a potentially fruitful direction and that the slowing is so modest it is unclear if it will be noticeable to patients and families. These medications also do not address other underlying causes for dementia such as vascular changes.

Conclusion:

These new drugs are exciting, but we do not think they are ready for "prime time" yet. These medications would require significant infrastructure change in New Zealand, as they need to be infused every two to four weeks for 18 or so months. They can have significant risks in the form of bleeding and swelling (ARIA – amyloid related imaging abnormalities), and so will need at least five MRI scans throughout treatment. Specific patient population appear to be more at risk of ARIA than others (those who have APOE 4 alleles or on blood thinners). There is also a question mark over the future safety of these medications in patients who will need

treatment with blood thinning drugs or antiplatelet medication (ie stroke, heart attack, atrial fibrillation). The current cost is around $ U.S 27,000 a year ($NZ45,000+) for the medications, with the investigations for treatment (amyloid PET scan, surveillance MRI's (at least 5), infusion costs, monitoring costs etc) as extras. The medications also have not been used outside of very strict trial related guideline. We are concerned that when these medications are used in the general population with lots of medications and medical problems, they will be associated with serious complications. Our preference would be to wait and see what happens.

These medications do not replace the lifestyle factors that can increase cognitive reserve and wellbeing.

References:

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