Alzheimer's
Drug Discovery
Foundation

Valacyclovir or Acyclovir Evidence Summary

What are Valacyclovir and Acyclovir?

Valacyclor and acyclovir are anti-viral drugs used to manage the various types of herpes viruses. Valacyclovir is a prodrug that is more orally bioavailable and gets broken down into acyclovir by the liver. The drugs inhibit viral DNA replication. The relevance to Alzheimer's is directly related to the viral infections, with some researchers speculating that chronic latent infections by these viruses can directly contribute to the development of Alzheimer's disease as well as inflammaging and immunosenescence.

Herpes Simplex Virus 1 (HSV-1) is a common and contagious virus that is most known for causing cold sores in humans. In between outbreaks, the virus can hide from the immune system inside neurons. During an outbreak, the latent virus reactivates and is transported down the neuronal axon to the skin, where new cold sores form. More than half of infected people who have the virus in their nervous system show no peripheral signs of the disease like cold sores (reviewed in [1]).

HSV-1 DNA is commonly found in the brains of elderly people although less so in younger people. Some researchers hypothesize that HSV1 periodically reactivates in the brain, for example during stress or inflammation or immune suppression, causing focal but cumulative damage. This periodic reactivation is assumed to be quite mild or it would lead to herpes simplex encephalitis, a rare but often fatal outcome.
Cytomegalovirus (CMV) is another herpes-related virus. In people with healthy immune systems, CMV infections often go unnoticed but, particularly in the elderly, the latent infection is hypothesized to sometimes become chronic, leading to accelerated aging and inflammation.

Additional herpes-related viruses related to chicken pox or HSV-2 (genital herpes) also embed inside neurons and can reactivate periodically but HSV-1 has been more extensively studied in the link to Alzheimer's.

Do Valacyclovir and Acyclovir provide neuroprotective benefit?

A reasonable theoretical rationale links chronic HSV-1 infection to Alzheimer's disease but studies are needed to test whether the anti-viral can make any difference to chronic reactivation and long-term brain health

Types of evidence:

- no RCTs or epidemiology on the use of anti-virals to prevent or treat AD or improve cognition
- 1 cell culture study on valacyclovir protecting against Alzheimer's pathology induced by HSV-1 viral stressor
- Modest indirect evidence for the target (eg. risks of HSV1 infection) from epidemiology and laboratory models

Human research on the use of antivirals to prevent or treat dementia and cognitive aging: *None*

Mechanisms of action for potential neuroprotection identified from laboratory and clinical research: Signs of HSV1 infection have been linked to Alzheimer's disease risk. People who have serum antibodies that reflect recent exposure or reactivation of the virus have a higher risk of developing Alzheimer's disease, for example with a 14-year hazard ratio of 2.55 (95% CI 1.38-4.72) ([2]). In contrast, antibodies that reflect lifelong exposure but not recent reactivation (IgG) do not associate with a higher risk of Alzheimer's disease (reviewed in [1]).

The association between viral reactivation and Alzheimer's disease risk might reflect direct damage to the brain by the virus, as suggested by the researchers. However, it might also be an artifact of residual confounding. Viral reactivation is known to be triggered by stress, inflammation, and immune suppression, all of which might also reflect an overall poor state of health.

HSV1 DNA has been detected in 90% of the plaques of Alzheimer's patients ([3]). Very small studies have reported that it is present in the brains of Alzheimer's patients at a slightly higher frequency than age-matched controls (eg. [4]). The difference in infection rate does not appear compelling; investigators argue that infection is sometimes asymptomatic. In other words, it is the highly variable response of the individual to the virus and the probability of a given strain to reactivate that leads to damage in some people but not others. While this explanation is credible, there is little strong evidence yet to back it.
In laboratory cells, HSV1 infection has been reported to cause beta-amyloid aggregation and tau phosphorylation. It may also inhibit autophagy, disrupt apoptosis regulation, trigger the release of proinflammatory cytokines, and increase oxidative stress (reviewed in [5]).

Even if HSV-1 infection and reactivation does drive Alzheimer's pathology, it is very unclear whether available anti-viral drugs would prevent the disease. Valacyclovir does have some brain penetrance, as shown by its ability to treat viral encephalitis. But these drugs do not remove the virus from within cells. What dose would be required to prevent the theoretical mild viral reactivations that are occurring inside the brain? Would vulnerable aging patients need to take anti-viral drugs daily? Weekly? For how long? Unless we can answer these questions, it will be difficult to design a clinical trial to conclusively test the viral hypothesis.

APOE4 interactions: APOE4 carriers reportedly have a higher risk of recurrent reactivation of HSV-1 cold sores and HSV-2 genital herpes ([6]). APOE4 carriers with HIV similarly have twice the risk for dementia and neuropathy compared to non-E4 HIV patients ([7]). However, APOE status had no effect on the relationship between HSV-1 antibodies and the risk of Alzheimer's disease ([2]). On the other hand, APOE2 carriers reportedly have a higher risk of strong CNS reactivation of the virus leading to encephalitis ([8]).

Safety: *Well-tolerated in clinical trials but some side effects can occur like headache, neutropenia, nausea, etc. However, long-term chronic use has not been adequately studied and would presumably be required for dementia prevention in vulnerable patient populations*

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Types of evidence:

- numerous clinical trials and postmarketing surveillance

Valacyclovir and acyclovir have good safety profiles overall. In clinical trials, the drugs have been well tolerated but with some side effects like headache, rhinitis, ([9]), and nausea, dizziness, abdominal pain, arthralgia, depression, and, in HIV-infected patients, fatigue (drugs.com). Drug interactions are not known to be a significant concern with Valacyclovir (drugs.com) but significant to serious interactions have been noted with bacitracin, talimogene laherparepvec, cimetidine, cobistat, emtricitabine, tenofovir (medscape).

Future research needed on the connection between virus infection and Alzheimer's disease and whether anti-virals may be of benefit: The rationale would be strengthened by better data on whether HSV1 reactivation does not just occur in Alzheimer's patients but occurs in early presymptomatic phases of the disease. Alzheimer's disease begins in the brain decades before symptoms become apparent so, if HSV1 reactivation is driving the pathology, it should be visible in apparently healthy people who have high levels of beta-amyloid plaques. Also, if HSV1 reactivation is helping to cause Alzheimer's rather than simply a consequence of an aging and vulnerable patient, it should be possible to show that HSV1 reactivation is not a global observation from other types of neurodegeneration like frontotemporal dementia, vascular dementia, multiple systems atrophy.

No clinical research is underway to our knowledge on an anti-viral drug for Alzheimer's treatment or prevention. The next steps will likely be a clinical trial looking at short-term biomarkers related to Alzheimer's disease. Unfortunately, if the trial fails, it will be difficult to interpret because there is little ability to test whether the drug adequately blocked viral reactivation.

In the long term, a vaccine against viral reactivation would be the most effective approach (eg [10]) but, to date, clinical trials for HSV vaccination have failed ([11]).

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