Inhibition of reverse transcription in type I interferon mediated neuropathology AGS-RTI

Lay summary of study results

Background

Aicardi-Goutières syndrome (AGS) is a very severe disease of childhood, particularly affecting the brain and the skin. There is a close link between AGS and increased amounts of a chemical called interferon. Interferon is normally only produced when we are infected by a virus. In AGS there is no viral infection. Instead, the cells in our body are confused into thinking that their own genetic material is coming from a virus. As a result, they produce interferon all of the time. We think that this interferon acts as a poison that damages the cells in the body. If that is true, obvious ways to treat AGS would be to reduce the amount of interferon and/or block its action.

Between 2015 and 2018 we undertook a clinical trial in AGS in Paris, using three drugs that we predicted might reduce interferon levels. These drugs (abacavir (ABC), lamivudine (3TC) and zidovudine (AZT)) are called reverse transcriptase inhibitors (RTIs). These are some of the same drugs that are used to treat HIV infection, the cause of AIDS; which means that they have been used in millions of people across the world, including babies and children. Because of this, we know that these drugs are extremely safe, and associated with very few side effects. In eight patients taking these three RTIs for a period of one year, we observed a fall in the level of interferon, which increased again when the drugs were stopped. These encouraging results suggested that we may have identified an important approach to treating AGS. In our recently completed trial in the UK, we used these same drugs, given individually (ABC or 3TC) and in combination (ABC+3TC+AZT: so-called 'triple therapy') for six weeks, and monitored the effect of treatment on the level of interferon signalling.

Results

Time to first and last patient recruitment was, respectively, 31 and 40 months following the trial start, with 13 patients recruited over a total study length of 54 months. Ten serious adverse events were recorded, none of which was thought directly related to treatment. One patient died after the first treatment arm of the study, and one patient was withdrawn at the beginning of the third treatment arm due to bowel perforation. Compliance with taking the drugs was poor in the triple therapy arm, with only four of 12 patients entering this final arm able to fully tolerate the prescribed dosing for six weeks. No statistically significant effects were observed with the use of either ABC or 3TC individually, or with ABC+3TC+AZT over six weeks. A statistically significant reduction of the IFN score was recorded after three weeks of ABC+3TC+AZT.

Interpretation

There is insufficient evidence from this trial that single therapy with ABC or 3TC is either effective or ineffective in reducing type I IFN signalling over a six-week period in selected AGS genetic subtypes. The effect of ABC+3TC+AZT at three weeks provides some support for the results of our previous clinical trial, although there was insufficient evidence of an effect at six weeks. These results should be interpreted with caution given difficulties with compliance and the low number of patients treated. Time to local Research and Development (R&D) approval, and time to Sponsor authorisation following R&D approval, severely limited patient recruitment.