

Summary of CARDIOMAN study results for participants and families

Background to the CARDIOMAN Trial

The major biochemical feature of Barth syndrome is a change in the levels of two lipids (fats) in the mitochondrial powerhouses of cells: cardiolipin levels are reduced and monolysocardiolipin levels increased. The resulting distorted ratio of these chemicals (termed the “cardiolipin ratio”) is dramatically different between people with and without the disease. Scientific studies at New York University (NYU) have shown that drugs including bezafibrate and resveratrol can improve this ratio, shifting it back towards more normal levels in both animal and human Barth syndrome cells. This is thought to be important because some people with Barth syndrome with better cardiolipin ratios have been reported to have less severe disease, with better exercise ability and mild or non-existent neutropenia.

Resveratrol is a food supplement sold in health food shops that has never been formally approved as a drug in children. By contrast, bezafibrate has already been approved, successfully tested in children and widely used for lowering lipid levels in adults. It has also been shown to improve cardiac failure in a mouse with an experimental form of Barth syndrome.

The CARDIOMAN trial was funded by the UK National Institute for Health Research (NIHR) to test whether bezafibrate could improve muscle and cardiac function and quality of life in boys and men with Barth syndrome under the care of the UK NHS National Barth Syndrome Service. Those entering the trial were given 4 months of either bezafibrate tablets or an inactive “placebo” tablet so that neither the participant nor the clinical team knew which one they were taking. After a month off medication they then switched to the other tablets for a further four months. The order in which participants received the bezafibrate and placebo was randomised. A wide range of tests were performed before starting and at the end of each treatment phase. Clinical results were also compared with the effects in the laboratory of both bezafibrate and resveratrol on blood cells donated by trial participants.

Eleven individuals aged 9 to 27 years were recruited from a potential clinic population of 20 aged 6 years or above. All results have now been analysed and are summarised below.

CARDIOMAN Trial results

Primary Outcome Measure:

Peak body oxygen uptake (also known as VO_2 max) can be measured whilst exercising at maximum effort on a bicycle and has been widely used in research studies to assess combined cardiac and muscle function in Barth syndrome; it has also been used in multiple trials of drugs to improve heart failure. This was therefore chosen as the primary outcome measure.

Unfortunately, it did not show a statistically significant improvement after taking bezafibrate.

Secondary clinical outcome measures:

Heart 'strain' measured by echocardiography was statistically significantly better with bezafibrate at rest, but not at peak exercise. Strain is a measure of heart muscle function. It is a very sensitive measure and improvements in strain are not always reflected in other more traditional parameters (such as ejection fraction). Because strain is a sensitive measure, an improvement does not always translate into a significant clinical improvement. Other echocardiography data suggested heart chamber sizes improved but the differences were not statistically significant. The tendency towards improvement was not confirmed in MRI studies performed in parallel. No other cardiac assessments showed significant changes. Despite these areas of cardiac improvement, quality of life did not change significantly.

Secondary blood and laboratory testing outcome measures:

Blood samples from participants were tested directly for specific outcome measures. Cells isolated from the blood were also tested with laboratory tests. With respect to the former, amino acid levels improved in participant's blood after bezafibrate treatment: cysteine levels were significantly higher, there was a trend to improved arginine levels but there was no significant change in neutrophil numbers. With respect to laboratory tests, no significant changes in mitochondrial size, number or function were seen in laboratory isolated cells after drug treatment. Consistent with the original NYU findings, improvements in cardiolipin ratio were seen when isolated cells were treated in the laboratory with bezafibrate or resveratrol; however, there was no significant change in cardiolipin ratio in participants' blood after bezafibrate treatment.

Summary

Interpreting the results of such a small trial is challenging, especially since it is rare to find statistically significant results for a primary outcome measure in such a small trial. Finding positive echocardiographic changes in this study is promising and interesting, especially following on from positive cardiac effects of the same drug in laboratory isolated cells, but this is tempered by finding no change in quality of life with bezafibrate.

It may be that longer duration or a higher bezafibrate dose might have produced better outcomes. It should be stressed that bezafibrate was tolerated well with only one boy stopping the drug 8 weeks into treatment due to gastrointestinal symptoms. The only other drug trial performed so far in Barth syndrome assessed the injectable drug elamipretide. Like CARDIOMAN, this trial also did not show a statistically significant improvement in the primary outcome (six-minute walk test) after 12 weeks. Most participants then participated in an extension study, during which all received the drug (so no control group). Over the 60 weeks of the extension study, improvements were seen in the six-minute walk test, muscle function and fatigue. This suggests that it could take much longer than the four months of therapy used in CARDIOMAN to achieve the maximum improvement in mitochondrial function.



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