

Title: ARAMIS: Anakinra versus Placebo in Acute Myocarditis
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Prof Montalescot

"So I'm Professor Montalescot, interventional cardiologist at Pitie Salpetriere, and I'm the president of the Action Group.

Dr Kerneis

And I'm Mathieu Kerneis. I'm a professor of cardiology at the Pitie Salpetriere hospital. And I'm also an interventional cardiologist. So ARAMIS is talking about acute myocarditis. So acute myocarditis is an inflammation of the heart, it affects young patients that are frequently hospitalised for the first time of their lives in the intensive care unit and these patients are exposed to a 3% risk of death and heart transplantation at one month when we have an all comers population, including either [indistinct] uncomplicated form of myocarditis.

The specific drug of ARAMIS is anakinra. So Anakinra is an antagonist of the receptor of IL-one. We have a rationale based on experimental studies and case reports in human suggesting that the inhibition of the IL-one pathway could be effective in acute myocarditis. And Anakinra is an antiinflammatory drug already used in many inflammatory disease such as rheumatoid arthritis or recurrent pericarditis with an acceptable safety profile. And we don't have good drugs for this disease.

Prof Montalescot

So far we give beta-blockers, ACE inhibitors but nothing really works for this patient. So we're trying to find something.

Dr Kerneis

I think one of the key points is that when you look at the previous studies there is only few studies on acute myocarditis. In fact there is the MTT trial back in 1995 and the

TIMIC trial in 2009 and both studies on wall patients with inflammatory cardiomyopathy not really acute myocarditis.

So we did an academic trial coordinated by the Action Group. It's a randomised, multicenter, double blind phase 2B trial while enrolling patients with a suspicion of acute myocarditis. And when we had a confirmed diagnosis based on CMR, patients were randomised between anakinra 100 milligramme on top of standard of care or placebo on top of standard care and all the treatment were administrated during the hospitalisation period and then patient were follow up during 28 days.

And we were looking at a patient centre outcome, the number of days free of any myocarditis complication. What is a myocarditis complication? It is heart failure, acquiring hospitalisation, chest pain, requiring new medication, ventricular arrhythmia or left ventricular dysfunction. We're also looking and it's important because it's a phase 2 trial, we're also looking to a safety endpoint, that is the rate of serious adverse events including those potentially related to the drug.

So first we enrol an all-comers population of acute myocarditis, mostly at low risk of event. And for the first time all patients had a diagnosis of myocarditis based on CMR. They were young, they were male, they had a history of recent infection and there was absolute no difference in the number of days free of any myocarditis complication between the anakinra group and the placebo group. When we look at the clinical event rates, there was a 10.5% event rate in the anakinra arm and a 16.7% event rate in the placebo group. We are not powered to draw any firm conclusion on this number. And when we look at the right of new chest, chest pain requiring new medication, there is a 3% event rate in the anakinra arm and a 10% event rate in a placebo group. There was no safety issue with anakina. I think it's an important message. In particular, there was no safety issue with serious adverse events related to the drug. And that's it.

Prof Montalescot

Yeah, I think it's a little bit disappointing because it's a neutral result, but we have some signals on symptoms especially that may be interesting for the future. And again, this

kind of studies is not easy to do. It's a rare disease in young patients and we need lots of centres to recruit a small sample size.

As you can see, the next step is probably to look at more severe conditions of myocarditis or maybe to treat longer the patients, but we will see other randomised studies in the field.

Dr Kerneis

So there is like two ongoing studies on acute myocarditis. There is a MIT trial led by Professor Amirati, which is the discussion today of the trial that is recruiting patients at high risk of event, patients with a feminine form of myocarditis that are randomised between corticosteroids and placebo. And there is also the ARGO trial, which is also an action group trial that will randomise 300 patients with a low to mid risk of event myocarditis. But this time we will treat patients for six months and try to have a better result than with [indistinct]. With another anti-inflammatory drug? Yes, with another anti-inflammatory drug, the colchicine targeting finally the same pathway.

Prof Montalescot

Yeah, so it's an inflammatory disease and we are looking for an anti-inflammatory drug working corticoids colchicine anakinra. We need to find something for these patients.

Dr Kerneis

For now, we are left with few effective treatments. With 120 patients, ARAMIS is the largest trial on acute myocarditis and on all patients at mostly at low risk of event, there is no difference between the two groups on the primary endpoint, but there is no safety issue. And interesting signal. Clearly this is not the end of the anti-inflammatory strategies for this patients."