Design of the Tocilizumab (TCZ) in Giant Cell Arteritis (GCA) Trial: A Summary in non-medical language

1. Introduction

This describes what GCA is and outlines the current standing with regard to treatment and the study of other drugs to reduce corticosteroid (CS) therapy (usually prednisolone in the UK). This paper describes the form of the Phase III trial to look at using TCZ in GCA.

2. Design and Methods (What they are doing and how)

This section starts by describing the role that the immune system is believed to play in triggering GCA.

Put very simply, many inflammatory conditions are due to the effect of substances called cytokines, of which there are several. One in particular, called IL-6, is known to make proteins that can change inflammation from an acute (short term) to a chronic (long term) state. It is found in increased amounts in the blood of patients with GCA and mirrors the disease activity – it goes up when the disease is active and goes down when enough CS treatment has been given to remove the inflammation. Many patients are familiar with the blood tests of ESR (erythrocyte sedimentation rate) and CRP (C reactive protein) which are often done to monitor their illness, the level of IL-6 is another similar test.

IL-6 increases in GCA because something has made the production line pathway in the body overactive so it is hoped that if you can put a brake somewhere on that pathway there will be less damage from inflammation. This theory has already been tested by giving between 20 and 30 patients TCZ (which is known to block this pathway) with good responses and no safety concerns being found. The next stage is to do the same thing in a larger group of patients for a longer time to look at how safe and effective TCZ is for treating GCA.

A total of 250 patients who fit specific criteria for the diagnosis of GCA will be put into 4 different groups. The patients must have had symptoms of active GCA in the 6 weeks before the first baseline visit. Both new patients and patients whose GCA has relapsed can be included and so can patients who have already been taking methotrexate for more than 6 weeks previously (but not other immunosuppressant drugs). The study will last for 52 weeks in what is called the “blinded” period when no-one, neither doctors nor patients, will know what medications are being given to which patient – everyone will get an injection and a pill. Every patient will be given steroid treatment in the same way that they would normally so no-one will be at any higher risk from their illness than they would be under their normal hospital care at present.

One group of patients will be given an injection (subcutaneously, that is just under the skin) of a standard dose of TCZ every week for a year whilst a second group will be given the same dose every second week. A third group will get an injection but it won’t have any TCZ in it. This is called a placebo group and is to see if there is a difference in the results achieved for the patients on the “new” drug or whether they might have got better anyway without it. All of these patients will get a dose of steroid throughout the study, with the dose being reduced in exactly the same way as they would normally and being monitored closely to make sure their GCA does not get worse. Two different rates of reduction will be used, one over 26 weeks and one over 52 weeks, but according to a

fixed timetable. The dose they are given at the start of the trial will be one which is suitable for their level of illness and if there is any sign of the GCA flaring during the trial the steroid dose will be adjusted suitably as it would be if they were not part of the trial.

After 52 weeks all the patients will be reviewed to assess the state of their illness: have they gone into remission? Remission means there is no sign of the disease being active – all their blood tests are in the normal range and they have no symptoms of GCA. All the patients will then be followed up for another 104 weeks to look at the long term safety and efficacy (how well it works) of TCZ , to see if a maintenance dose is needed and how effective it has been in reducing the amount of CS they need to take in the long term. Anyone who still has symptoms or if their symptoms return will be offered the TCZ injection as well as their CS dose.

The study is being carried out in the USA and in Europe in 100 different places. It is being funded by the drug company that makes TCZ with some support from the Arthritis Foundation. Every patient will have the procedure explained to them and will have to sign that they have been told all they need to know and been able to ask questions.

All the results will be analysed using statistical methods to see if various expected endpoints have been reached successfully or not. These include time to remission (no signs or symptoms of GCA), total dose of steroid, when flares occurred, which version of giving TCZ appears better, how safe was it for the patients and so on.

3. Discussion and Conclusion

In this section they talk about the current standard of care for GCA – which, as most patients are aware, varies greatly from hospital to hospital and even doctor to doctor. This leads to problems in looking at a new prospective treatment and deciding if it is better than what is being offered at present. GCA itself has many risks, the only option for treatment at present, steroids, also potentially have risks which are greater the more of the drug is given. More than 4 in 10 patients with GCA relapse as their dose is reduced. In aiming to keep the total steroid dose as low as possible, the risk of the disease returning is often increased.

The aim of any trial is to find a better answer to the symptoms or outcome of the disease. In this case, it is known that remission can be achieved using steroids – is it possible to achieve it safely, in a more reliable way, faster or at a meaningfully lower total steroid dose using an additional drug even though it will cost considerably more (whatever it is, a new drug is likely to be expensive). It is hoped this study will provide proper answers to these questions, and more, for this particular drug.

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