Add-on low-dose prednisolone has beneficial long-term effects in seniors with established rheumatoid arthritis

**INTRODUCTION**

Rheumatoid arthritis is a chronic inflammatory disease that affects a person’s joints, and may cause pain and disability. Rheumatoid arthritis can affect people of all ages, but it most often starts between the ages of 40 and 60. Rheumatoid arthritis is more common in women than men.

Glucocorticoids are a type of medicine used to treat rheumatoid arthritis. It has been shown that glucocorticoids such as prednisone or prednisolone can quickly stop inflammation and improve pain and function in people with rheumatoid arthritis. Trials of glucocorticoids in rheumatoid arthritis are rare, and few have been done according to current quality standards. Additionally, many trials exclude older people or those with other diseases alongside their rheumatoid arthritis. Almost all clinical trials have shown benefit for glucocorticoids, and none has flagged substantial risks. In contrast, observational studies of people taking these medicines in the real world consistently show increased risks and side effects.

**WHAT DID THE AUTHORS HOPE TO FIND?**

The authors wanted to investigate the balance of benefit and harm of low-dose prednisolone in a population of older people with rheumatoid arthritis.

**WHO WAS STUDIED?**

This study looked at 451 people with rheumatoid arthritis. Everyone was over the age of 65, and had other health conditions as well as their rheumatoid arthritis.

**HOW WAS THE STUDY CONDUCTED?**

GLORIA was a randomised, double-blind trial, which means that patients were assigned by chance to one of two treatment groups to receive either prednisolone tablets (5 mg per day), or placebo. Using chance in this way means the groups are similar and allows the variable or treatment under investigation to be compared objectively. During the treatment neither patients nor their doctors knew which group they were in.

GLORIA was also a pragmatic study. This means the study tried to mimic how people might be treated in everyday, normal clinical practice. For this reason, everyone taking part could also take other medicines for their rheumatoid arthritis as recommended by their doctor, such as biologics or steroid injections, and they were allowed to change that additional treatment when needed. It was also recommended that everyone take calcium and vitamin D supplements. The trial followed people for 2 years.

The study measured disease activity to see the benefits of treatment. To measure the harms, the researchers recorded how many people had an adverse event of special interest. These included side effects (except worsening of disease) that led to a person withdrawing from the trial, as well as bone fractures, cardiovascular events such as heart attacks, and new diagnosis of hypertension (high blood pressure), diabetes, infection, cataracts, and glaucoma that required treatment.

**WHAT WERE THE MAIN FINDINGS OF THE STUDY?**

The main finding was that people taking prednisolone had a marked benefit and saw improvement in the signs and symptoms of their rheumatoid arthritis. While the disease activity score was similar (4.43 in the prednisolone group, and 4.60 in the placebo group), overall disease activity after 2 years was 0.37 points lower on prednisolone, and joint damage progression was 1.7 points lower compared to placebo.

The trade-off was that 24% more people taking prednisolone had at least one adverse event of special interest. Most of these events were infections of mild to moderate intensity. There was nothing to suggest that there was an increased risk for bone loss or cardiovascular events.
The authors think this is most likely the upper limit of harm to be expected if people take the 5 mg dose for 2 years under the care of a rheumatologist. Importantly, it is much lower than the estimates from observational studies.

ARE THESE FINDINGS NEW?
Yes. This is the first large pragmatic trial of glucocorticoids added to standard of care in rheumatoid arthritis, the first large treatment trial in seniors with the disease, and one of the first to study and demonstrate long-term effects of glucocorticoids on disease activity and damage progression in people with established rheumatoid arthritis.

Previously it was thought that prednisolone had only a temporary effect when taken on top of other antirheumatic treatments, and the long-term side effects were thought to be unacceptable. The results from GLORIA prove that these assumptions are false.

WHAT ARE THE LIMITATIONS OF THE STUDY?
There are some limitations to the GLORIA study. The pragmatic design is both strength and weakness, since the results are immediately applicable to the target population, but long-term treatment benefits were probably underestimated.

The authors also note that a substantial proportion of people (38%) stopped the study prematurely, mostly for ‘trial fatigue’ and problems accessing care due to the COVID pandemic, so the average time people were treated for was 19 months. Also, the design allowed people to take co-treatments, but this became difficult to compare between the two groups.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?
The authors hope these results will be picked up by guideline committees, and that prednisolone will be allowed a more prominent place as a regular drug in the treatment of people with rheumatoid arthritis. Several reports on the trial are underway, including assessing cost-effectiveness, and looking at how well people did once they came off the prednisolone after the trial. The authors are also making the information available as open data for all researchers to use in their own studies.

WHAT DOES THIS MEAN FOR ME?
If you have rheumatoid arthritis and are over the age of 65, you may be prescribed low-dose prednisolone – not only for brief periods of ‘bridging’ at the start of antirheumatic treatment or to treat flares – but also as a long-term option. The results from GLORIA confirm that the benefits of long-term use outweigh the potential risks, as long as treatment is responsibly managed and you are monitored regularly for side effects. It is important that you take your medicine exactly as prescribed, and do not change the dose or stop taking it without talking to your doctor first.

If you have any concerns about your disease or its treatment, you should talk to your doctor.

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