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Glucocorticoids in early rheumatoid arthritis

This series of articles facilitated by the Australian Cochrane Musculoskeletal Group (CMSG), aims to place the findings of recent Cochrane musculoskeletal reviews in a context immediately relevant to general practitioners. This article considers treating patients in the first 2 years of rheumatoid arthritis with low dose oral corticosteroids.

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology that according to self reported data from the Australian Bureau of Statistics affects 2.4% of the Australian population.[1] Without treatment it results in joint deformity and destruction leading to significant disability and decreased quality of life. It may also shorten life expectancy with increased deaths due to cardiovascular disease, infection and cancer.[2]

Glucocorticoids are often used in addition to disease modifying antirheumatoid drugs (DMARDs) in the treatment of RA but their value is still debated. Proponents have argued that while high doses are associated with well known adverse consequences, in low doses (equivalent ≤10 mg/day prednisolone) the modest risks may be outweighed by significant benefits of rapid symptomatic relief,

Table 1. Key review results[2]

- Fifteen randomised controlled trials were identified with a total of 1414 participants. Gender and mean age was not specified and median or mean duration of disease was only specified for two trials. Most trials studied early RA (disease duration 1–2 years, although mean disease duration was 13 years in one study). Two studies only included participants aged <60 years while one trial only included participants aged ≥60 years
- There was wide variation in daily and cumulative doses of oral glucocorticoid. Some studies used a fixed low dose glucocorticoid (up to 7.5 mg/day prednisone equivalent). Several studies started with higher doses and titrated down over weeks or months to the lowest dose needed to control symptoms. Individuals received 270–5800 mg (mean 2300 mg) of prednisolone equivalent glucocorticoid over the first year of treatment. The duration of glucocorticoid treatment ranged 6–24 months
- Most participants were prescribed DMARDs as well as glucocorticoids
- Study duration varied from 1–2 years, with 806 of the participants having radiological follow up at the maximum study duration of 2 years. The outcome measures were standardised scores for erosions and joint space narrowing on X-ray of the hands, or hands and feet, at 1 and 2 years
- Patients treated with glucocorticoids had substantially less joint damage at follow up at 1 and 2 years. The proportion of benefit gained by glucocorticoids in reducing the progression of erosions from an average of all the studies over 1 year was 67.2% (CI: 48.9%, 85.4%) and over 2 years 61.3% (CI: 46.5%, 76.1%). This benefit was over and above any benefits from DMARDs
- This radiological benefit was demonstrated for all treatment combinations: glucocorticoids with and without DMARDs and/or nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoid treatment duration for <26 weeks or longer, and with the constant low dose or step down glucocorticoid regimens
- Harms of treatment were not reviewed

suppression of disease activity and slowing of radiological progression.

Kirwan et al[3] performed a systematic review to assess the efficacy of glucocorticoids in inhibiting the progression of radiological damage in adults (>18 years) with a diagnosis of RA. The review results are summarised in *Table 1* and how these results might affect practice are shown in *Table 2*.

Conclusion

It is clear that low dose glucocorticoids do have a beneficial effect in early RA through their ability to provide symptomatic relief and reduction in joint damage. However, applying these results to clinical practice is not straightforward as the Cochrane review only established benefits and did not address risk.

There are still many unanswered questions about the use of low dose glucocorticoids in RA, including the optimal dose and duration of treatment and the true risks of adverse effects over the longer term. People with RA are already at an increased risk of cardiovascular disease and osteoporosis as a result of their disease. If oral glucocorticoids are to be used, other drugs that increase steroid induced gastrointestinal and cardiovascular toxicity such as NSAIDs should be avoided. The difficulties in being able to withdraw even low dose glucocorticoids in routine clinical practice – and the concomitant risks associated with longer than planned use – should not be underestimated. Furthermore, their value in long standing RA disease is unknown and the benefits need to be carefully weighed against the potential for harm in patients with or at risk for obesity, osteoporosis, diabetes, hypertension, glaucoma and heart disease.

In view of the many unresolved issues, the use of low dose oral glucocorticoids should be reserved for patients with severe active RA and restricted to short term use. We strongly advise consultation or discussion with a rheumatologist before commencement of oral glucocorticoids for the treatment of RA.

Conflict of interest: none declared.

References

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Table 2. Putting evidence into practice

Case study

Anna O'Dell, 38 years of age and previously well, presents with a 6 week history of pain and swelling in the joints of her hands, feet, knees and shoulders associated with marked stiffness, particularly in the morning. NSAIDs have not helped greatly. You arrange for an early referral to a rheumatologist who, like you, suspects she has RA. The rheumatologist recommends she commence a standard DMARD regimen but explains that it will take some weeks before she could expect any improvement. In the meantime, the rheumatologist suggests that she could simply continue to take NSAIDs and/or simple analgesics if the symptoms are not significantly bothering her. If she needed more immediate symptomatic relief, other options included steroid injections into the most troublesome joints or low dose oral glucocorticoids (eg. prednisolone 5.0–7.5 mg in the morning) although the potential risks and benefits would need to be carefully considered. Anna opts to wait and see how she goes with the DMARDs alone.

Two weeks later Anna returns to see you because her symptoms are worse and she is finding it increasingly difficult to work. She tells you that she is not keen on injections but wants to know what you think about taking the prednisolone as she has heard that it can cause a lot of side effects. What do you advise her?

You acknowledge that this is a difficult and complex issue and that research has not provided clear guidance about the best course of action. You explain that in addition to relieving her symptoms it was shown in a recent Cochrane review that taking a low dose of prednisolone in the early stages of RA can assist the other drugs in protecting her joints from damage. In some studies patients only needed to take prednisolone for 6 months to protect the joints for 2 years. However, these benefits need to be carefully weighed up against the potential risks.

While the Cochrane review did not address risks, a paper by some of the same authors reviewed the evidence on adverse effects of ongoing glucocorticoid treatment in doses of 10 mg or less of prednisolone (or equivalent).[4] In brief, the major risks appeared to be a doubling of the already increased risk of osteoporosis, an increase in blood glucose which may result in diabetes in susceptible people, fat redistribution leading to moon face, and increased abdominal girth and increase in body weight. Cardiovascular risk, already increased in people with RA, increases with higher glucocorticoid doses. However, cardiovascular risk was not found to be altered at doses <7.5 mg/day prednisolone in the reviewed trials although the maximum follow up period of 2 years may have been too short for the development of cardiovascular events. There was no evidence to support alternate day dosing. While most of these effects are reversed when the prednisolone is stopped, you explain that some people find it hard to stop taking prednisolone as it controls their symptoms so well.

You explore why Anna is not keen on injections and explain that injecting steroids into the most troublesome joints may be just as beneficial but that the long term risk of toxicity is likely to be much less as the overall dose of steroid is likely to be much smaller.
Anna thinks it over and decides that she would like to try steroid injections. You call the rheumatologist who agrees that joint injection is appropriate.