REVIEW ARTICLE

Low-dose glucocorticoid therapy in rheumatoid arthritis. A review on safety: published evidence and prospective trial data

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Toxicity data from four prospective trials of low-dose glucocorticoid therapy in R.A.

Box start———————————————————————————————————

Box 1. Description of trials

The ARC low dose glucocorticoid study (ARC)[1, 2]

A double blind, randomised controlled trial over 2 years followed by 1 year double blind follow-up in 128 patients with rheumatoid arthritis diagnosed for less than 2 years. Patients had active disease and were allocated equally to prednisolone 7.5♣mg daily (in specially prepared tablets) or placebo. All other treatments except oral glucocorticoids were permitted and in practice most patients were treated with non-steroidal anti-inflammatory agents and second line anti-rheumatoid treatment.

The "low-dose prednisolone therapy" study (LDPT)[3]

In this double blind study 192 patients with active rheumatoid arthritis of duration less than 2 years who had not been treated before with intramuscular gold or methotrexate were equally and randomly allocated to one of two treatment strategies for two years: 1) 5♣mg prednisone once

daily in the morning and either intramuscular gold (50♣mg gold sodium thiomalate/week up to a total dose of 1000♣mg, thereafter 50♣mg every 2♣weeks) or methotrexate (7.5♣mg weekly for the first 3♣weeks, thereafter 10–15♣mg weekly; no folate supplementation) 2) placebo and intramuscular gold or methotrexate as above. Therapy with bisphosphonates, calcitonin, estrogens and fluorides was not allowed.

The utrecht prednisolone trial[4]

In this double blind study 81 patients with rheumatoid arthritis of duration less than 1 year were equally and randomly allocated to one of two groups of treatment for two years: 1) 10♣mg prednisone once daily at breakfast, 2) placebo in the same way. NSAIDs and analgesics were permitted and all patients received 500♣mg elementary calcium in the evening. After 6♣months sulfasalazine rescue medication was permitted.

The west of scotland early rheumatoid arthritis trial (WOSERACT)[5]

In this double blind study 167 patients with rheumatoid arthritis of median disease duration 12♣months (range 2–84♣months) were equally and randomly allocated to one of two groups of treatment for two years: 1) 7♣mg prednisolone once daily plus sulphasalazine (dose target 40♣mg/kg in both arms. Medians achieved (and range): 2.5♣g (1–4♣g) in both arms) 2) placebo prednisolone and sulphasalazine. At 2 years, in the prednisolone group 61 patients were still on prednisolone and 59 patients still on sulphasalazine. In the placebo group at 2 years 65 patients were still on placebo prednisolone and 53 still on sulphasalazine. The use of drugs for prevention of osteoporosis was left to the discretion of the rheumatologist: it was greater in the active group, although physicians were blind to treatment.

Box end————————————————————————————————————

Musculoskeletal adverse effects

Osteoporosis

Box start————————————————————————————————————

Box 2. Osteoporosis data from trials: Bone loss and fractures

ARC results[1, 2]

Results are available for 21 patients (Prednisolone=11, Placebo=10) who had bone mineral density (BMD) measurement because they were attending study centres where measurement facilities were readily available at the time of the study. Mean (SD) percentage reductions in BMD in the spine of the prednisolone group were 1.61 (4.98) and 2.96 (5.59) after 1 and 2 years respectively while in the placebo group the percentage reductions were 2.27 (5.54) and 1.29 (4.64) (not significantly different). In the hip the prednisolone group percentage reductions were 2.16 (7.07) and 1.19 (3.16) after 1 and 2 years respectively while in the placebo group the percentage reductions were 0.56 (5.62) and 4.02 (2.45) (P=0.04 at 2 years).

LDPT results[3]

X-rays of the lumbar spine among patients in prednisolone group (n=59) revealed two fractures at baseline, and one additional fracture at 24♣months (n=46). Among patients (n=64) in the placebo-group, there were at baseline two fractures, and at 24♣months (n=53) two additional fractures. The fractures were located at L1 (n=2), L2 (n=3) and L3 (n=2).

Utrecht results[4]

In the two years, T-scores mean (se) of the lumbar spine in the prednisone group changed from −0.8(0.3) to −1.1(0.3) and in the placebo group from −0.7(0.3) to −0.6(0.3). For the femoral neck T-scores changed from −1.8(0.2) to −1.9(0.2) and from −1.9(0.2) to −1.9(0.2), respectively. This were all non significant intra and between group differences. So, for the lumbar spine at 2 years, the difference between the T scores of the two groups was 0,5 in favor of the placebo group; this was unchanged at follow-up at 3 years. At 3 years, the cumulative number of fractures in the spine in the prednisone group was twice that of the placebo-group (10 versus 5). Doubling of the fracture rate has been described for changes in the T score of 1; this suggests that the double

fracture rate in the prednisone group was also partly due to structural changes of bone in the prednisone group.

WOSERACT results[5]

In the 2 years, median lumbar bone density in the prednisolone group changed from 1.079 at baseline to 1.073♣g/cm^2; in the placebo group bone densities were 1.157 and 1.280♣g/cm^2, respectively. For the femoral neck, bone density in the 2 years changed from 0.900 to 0.881♣g/cm^2 in the prednisolone group and from 0.927 to 0.911 in the placebo group. There were no statistically significant differences between the two groups at both points in time, nor statistically significant changes within groups.

Box end———————————————————————————————

Endocrine and metabolic adverse effects

Glucose intolerance and diabetes

Box start———————————————————————————————

Box 3. Hyperglycaemia data from the trials: blood and urine glucose levels

ARC results[1, 2]

No patient in the prednisolone group (n=61) developed diabetes mellitus, but one patient in the placebo group (n=67) did so.

LDPT results[3]

In the prednisolone group serum glucose levels of 34 patients (per protocol population) were measured 2♣hours after the last meal; at baseline and at 2 years, means (se) were the same: 5.6 (0.2)♣mmol/l. In the placebo group, mean (se) serum glucose levels of 42 patients (per protocol population) were 5.3 (0.2) at baseline and 5.1 (0.2)♣mmol/l at 2 years. In addition, the values for the so-called intention-to-treat population are given: prednisolone group (n=74): baseline value 5.7 (0.1) and after 24♣months 5.6 (0.3)♣mmol/l, placebo-group (n=81): at baseline 5.9 (0.2) and at 24♣months 5.5 (0.3)♣mmol/l.

Utrecht results[4]

In contrast to the placebo group, the mean (SD) serum glucose level increased significantly in the prednisone group, from 5.1 (0.6) at baseline to 5.9 (1.9)♣mmol/l at 2 years, p= 0.01. Hyperglycemia, as defined by the World Health Organization, developed in 2 patients in the prednisone group (n=40) and 1 in the placebo group (n=41).

WOSERACT results[5]

One patient in the placebo arm was on treatment for diabetes mellitus at the outset and 2 years. No patient required introduction of this therapy at 2 years (neither in the placebo nor active treatment group).

Box end——

Endocrine and metabolic adverse effects

Fat redistribution, body weight and growth

Box start——

Box 4. Weight gain trial data

ARC results[1, 2]

Both groups increased in weight, but there was no statistically significant mean increase in body weight in either group. One patient in the study had relevant weight gain; this patient had been allocated to prednisolone.

LDPT results[3]

Weight gain was assessed for the intention-to-treat population: 80 patients in the prednisolone group and 85 patients in the placebo group. Body weight in the prednisolone group increased from a mean (se) of 71.7 (1.4)♣kg at baseline to 76.7 (2.0)♣kg at 2 years, p<0.05; in the placebo group the numbers were 73.1 (1.7)♣kg at baseline and 73.4 (2.3)♣kg at 2 years. The difference at two years between the two groups was statistically significant.

Utrecht results[4]

In the 10♣mg prednisone group (trial methodology: see above) body weight increased significantly from baseline: the mean (sd) rose from 77 (19) to 80 (20)♣kg at 2 years, p=0.001; in the placebo group there was no statistically significant difference in time.

WOSERACT results[5]

In the 7♣mg prednisolone group (trial methodology: see above), body weight increased from 68♣kg at year 0 to 71♣kg at year 1 and 72♣kg at year 2 (Wilcoxon 0–1 year and 0–2 year p<0.001). In the placebo group weight increased from a median of 69♣kg at time 0 to 70♣kg at year 1 and 72♣kg at year 2 (Wilcoxon 0–1 year p=0.162, 0–2 year p<0.05). There were no statistically significant differences between the two groups at any point in time.

Box end

Cardiovascular adverse effects

Hypertension

Box start

Box 5. Hypertension data from trials

ARC results[1, 2]

On the group level: there were no significant increases in blood pressure in either group. On the patients' level: two patients in the prednisolone group (n=61) developed hypertension versus one patient in the placebo group (n67).

LDPT results[3]

At the start of the study, mean (se) blood pressure values (systolic/diastolic) were 128(2)/79(2) mm Hg in the prednisone group (n=34) and 130(3)/80(2) in the placebo group (n=42). At two years, these numbers were 141(4)/85(2) and 140(4)/86(2), respectively: no statistically significant differences between the two groups at both points in time, nor statistically significant changes within the groups. For the intention-to-treat population (prednisolone group n = 80 and placebo group n=85) the data were as follows. Prednisolone group baseline values:128(2)/78(1);

at 24♣months 141(3)/84(2). Placebo-group baseline values 128(2)/79(1); at 24♣months 140(4)/85(2). In the prednisolone group 6 patients (6%) developed hypertension (as stated by the physician) compared to 2 patients (2%) in the placebo group.

Utrecht results[4]

Patients with severe hypertension were excluded from this study. At the start of the study 11 patients in the placebo group and 5 in the prednisone group were normotensive under medication for their essential hypertension and they remained stable during the study. The numbers of patients with newly developed hypertension during the study were about equal: 7 in the prednisone group and 6 in the placebo group.

WOSERACT results[5]

At the start of the study, median blood pressure values (systolic/diastolic) were 140/80♣mm Hg in the prednisone group and 135/80 in the placebo group. At two years, these numbers were 140/80 and 130/80, respectively: no statistically significant differences between the two groups at both points in time, nor statistically significant changes within the groups. However, the participating rheumatologists were proactive in initiating antihypertensives as required and more patients were on antihypertensives in both the placebo and active groups than at the outset of the study (placebo 12 time 0, 16 at 2 years; active 10 time 0, 13 at 2 years).

Box end————————————————————————————————————

Ophthalmological adverse effects

Box start————————————————————————————————————

Box 6. Ophthalmological data from trials

LDPT results[3]

In the prednisolone group, 3 patients got glaucoma versus no patient in the placebo group; in the prednisolone group, 5 patient acquired cataract versus 6 patients in the placebo group; in both groups, less than 50% of patients was screened for ophthalmologic adverse effects, however.

Utrecht results[4]

In the prednisone group, 1 patient got glaucoma versus no patient in the placebo group; in both groups, 1 patient acquired cataract.

Box end——

Gastrointestinal adverse effects

Box start——

Box 7. Gastrointestinal data from trials

ARC results[1, 2]

No patient with relevant peptic ulcer disease was reported.

LDPT results[3]

In this study, patients with recent gastric and intestinal ulcers were excluded. Gastric distress was seen in the prednisolone group (n=93) in 9 patients (10%), versus in 4 patients (4%) in the placebo group. A gastric ulcer was detected in 3 patients in the prednisolone group (3%), but in none of the patients in the placebo group.

So, a higher rate of peptic ulceration and their complications due to low to medium dose glucocorticoids is not supported by these data.

Utrecht results[4]

In the prednisone group, peptic symptoms leading to gastroscopy occurred in 7 patients versus 3 in the placebo group, but ulcer with bleeding at gastroscopy was found in 1 patient in the prednisone group versus 2 in the placebo group.

WOSERACT result[5]

One GI bleed occurred in the active steroid group, none in the placebo group. No other patient had relevant peptic ulcer disease.

Box end——

Infectious adverse effects

Box start

Box 8. Infection trial data

Utrecht results[4]

Seventeen infections, treated with antibiotics occurred in 14 patients in the prednisone group (n=40) over the 2 years versus 22 infections treated with antibiotics in 15 patients in the placebo group (n=41).

WOSERACT results[5]

No excess of infections was documented in the prednisolone group compared to the placebo group.

Box end

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