REVIEW ARTICLE

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

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Introduction

The spectrum of toxicity of chronic glucocorticoid therapy is exhaustively reviewed in this article. However, less is known about the acute changes in routine monitoring parameters in patients with rheumatoid arthritis (RA). We reanalyzed the monitoring data of the COBRA trial that compared the combination of step-down prednisolone, low –dose methotrexate (MTX), and sulfasalazine (SSZ) to SSZ alone in early RA. This analysis demonstrates the highly consistent changes induced in many of these parameters, but also a relatively low yield in terms of findings requiring changes in therapy.

Methods

The COBRA ("COmbinatietherapie Bij Reumatoide Artritis") trial was a multicenter randomized double-blind controlled trial of 56♣weeks duration in patients with early active RA.[1] Application of the exclusion criteria resulted in a fairly healthy group (apart from the RA): we excluded patients aged below 18 or over 70, those with serious comorbidity or recent (3♣months or less prior to inclusion) major surgery, with active infectious disease, with a history

of tuberculosis, recurrent infections, recent (<3♣months) gastritis or gastrointestinal ulceration, any history of gastrointestinal bleeding or neoplasia. We also excluded patients with diabetes mellitus, hypertension treated with more than one antihypertensive drug, significant cardiovascular disease, liver disease, cataract, glaucoma, hematologic disorders, partial or total colectomy, reduced renal function (creatinine clearance <50♣ml/h), proteinuria (>0.5♣g/day), hypoalbuminemia and chronic dermatitis. Finally, we excluded patients on treatment with phenytoin, phenylbutazone, salicylates, barbiturates, cholestyramine, probenecid, oral anticoagulants (dicumarol derivatives), and patients with a history of alcohol or substance abuse.[1]

COBRA treatment comprised a starting dose of prednisolone of 60♣mg/day, rapidly tapered to 7.5♣mg/day within a time period of 6♣weeks, continued unchanged for 20♣weeks, and then withdrawn completely after 26♣weeks; 2) a low dose of MTX (7.5♣mg/week in one gift) for 40♣weeks, and then withdrawn in 4♣weeks; and 3) a maintenance dose of SSZ 2000♣mg/day. All patients received folic acid supplements (1♣mg/day), and calcium supplements (500♣mg daily); and/or vitamin-D supplements (25-(OH)-vitamin-D) (400 IE daily) were prescribed if necessary. Patients randomized to the SSZ monotherapy group received a maintenance dose SSZ (2000♣mg/day) as well as the supplements mentioned above.

Monitoring schedule

Patients were seen weekly in the first four weeks; then at weeks 6, 9, and 12; and every 4♣weeks thereafter. At every visit patients were questioned for adverse events; body weight and blood pressure were recorded. Blood and urine samples were examined: more than 20 tests in total at 19 time points, i.e. almost 400 tests per patient in the 56♣weeks of the trial (see results). Bone mass was measured every half year.

Analysis

Results of monitoring per treatment group are presented as mean (95% confidence interval) in line graphs over time. The initial period is magnified to better depict the changes. To correct for baseline differences, body weight is expressed as change. In each graph, the “Null Zone” indicates the area in which group means should fall if there is no significant difference at the 5% level (two-sided p value >0,05).[2] In other words, observed means falling outside this zone differ significantly from each other. As these analyses are exploratory no correction for multiple testing was applied.

Results

Clinical results

The main findings of the COBRA trial have been published previously.[1] Briefly, COBRA treatment (76 patients) caused almost immediate and strong improvement in disease activity, resulting in similarly strong and significant functional improvement assessed at week 16. Single treatment with sulfasalazine (79 patients) caused lesser but also significant improvement at week 16. Both treatment groups improved further up to week 28. Most of the clinical difference between the groups disappeared when prednisolone was subsequently withdrawn, with no further change after withdrawal of methotrexate. At week 28, the combination therapy group had significantly less progression of radiographic joint damage compared to the sulfasalazine group. Recently we have shown that progression remains slower in the COBRA group up to 4.5 years, i.e. 3.5 years after withdrawal of prednisolone.[3]

Toxicity

Significantly less patients stopped COBRA than sulphasalazine: 6 (8%) versus 23 (29%) (p=0.0008), and COBRA patients dropped out later (Figure 1). Differences were apparent for both toxicity and lack of efficacy. For instance all 4 efficacy dropouts in the COBRA group occurred after week 28, when prednisolone and methotrexate were stopped; in contrast, most of the 19 dropouts in which loss of efficacy played a role in the sulphasalazine group occurred

before week 28 (Figure 1). The adverse reactions that led to withdrawal of 2 patients in the COBRA group were: gastrointestinal tract complaints and dyspnea (final diagnosis exacerbation of chronic bronchitis). Adverse reactions that led to withdrawal of 8 patients in the sulphasalazine group were skin rashes in 4 patients, gastrointestinal tract complaints in 2 (one with concurrent proteinuria), granulopenia with concurrent increase in aminotransferases in one patient, and thrombopenia (diagnosis preleukemic disease) in the remaining patient.

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Figure 1 **Patients remaining in trial and reasons for dropout, per treatment arm**. COBRA treatment protocol is shown at the bottom of the graph. AE, adverse event; LoE, loss of efficacy; viol, protocol violation.

The study medication was discontinued and restarted at an adjusted dose according to protocol in 5 patients. Three of these 5 patients (1 from the COBRA group) had low granulocyte counts, the other 2 patients (in the COBRA group) had elevated aminotransferases and gastrointestinal complaints, respectively. The remaining adverse events were not followed by withdrawal of study medication. These included 18 cases (12 COBRA) of infection, treated on an outpatient basis, 17 cases (9 COBRA) of gastrointestinal complaints (no ulcer or bleeding); 10 cases (6 COBRA) of cardiovascular disease; including 1 myocardial infarction; and 11 cases (5 COBRA) of skin disorders. Various other symptoms, signs and transient laboratory abnormalities were reported in 37 cases (20 COBRA).(1) Thus, a total of about 62000 tests (400*155) not including confirmatory procedures were performed to detect relevant toxicity in a total of 7 patients.

Bone mass

In the first 28♣weeks, mean (95% c.i.) lumbar bone density change in the COBRA group (n=64) was −1.2% (−2.0, −0.3) versus 0% (−0.9, 0.9) in the sulphasalazine group (n=62) (p=0.06). In 56♣weeks, changes were −1.3% (−2.3, −0.4) and −0.3% (−1.4, 0.8) respectively, p=0.15. In the femoral neck corresponding bone density changes over 28♣weeks were –0.6 (−2.1, 0.9) versus –

0.7 (−2.1, 0.7); over 56♣weeks −1.9 (−3.1, −0.7) versus −1,3 (−2.5, −0.1; both: p>0.2. Eight versus 6 patients lost more than 5% (mean 8%) of spinal bone; 14 versus 9 lost more than 5% (mean 8%) of femoral neck bone. These losses typically occurred in the first half year, with stabilisation or improvement thereafter.[1]

Diabetes

For this study, patients with concomitant diabetes mellitus were excluded. In all patients, regularly urinanalysis for glucose was performed; positive glucose reactions were extremely rare.

Weight

Only during the first half year of therapy, the COBRA treatment group in which high to intermediate doses of glucocorticoids were used gained statistically more weight than the sulphasalazine alone group. After about one year (56♣weeks), the weight gain from baseline was 1.7♣kg in the combined treatment group (in which prednisone had been stopped) and 1.2♣kg in the sulphasalazine alone group, a non-statistically significant difference.

Upper GI

In the COBRA trial, patients with a history of gastrointestinal bleeding or recent (<3♣months) gastritis or gastrointestinal ulceration were excluded. In the COBRA strategy group and sulfasalazine alone group, gastrointestinal complaints occurred, probably at least due to sulfasalazine and/or methotrexate, but no ulcer or bleeding took place. A relevant finding from the economic study that ran alongside the trial: cost savings occurred because many patients in the COBRA group stopped taking NSAIDs and gastroprotection.

The results of routine monitoring are shown in Figure 2 (blood pressure, weight gain, and selected blood chemistry) and Figure 3 (hematology). In Figure 2 ESR is shown as reference outcome measure for disease activity, and in both the prednisolone dosing schedule is shown at bottom. Apparent from almost all graphs is an almost immediate change in the COBRA group,

followed by a slower change in the SSZ group. Within the groups the changes in many measures were highly consistent, resulting in strongly significant differences between the groups. These differences became less and mostly disappeared after the prednisolone was stopped, similar to the main outcome measures. Especially notable are the rapid (but limited) weight gain, the biphasic pattern in the platelet count, the rapid increase in hemoglobin and the increases in serum creatinine in both groups. More in line with expectation is the leukocytosis, granulocytosis, lympho– and eosinopenia. The changes in alkaline phosphatase are mainly attributed to changes in bone turnover, as there were no relevant changes in the liver function tests (gammaglutaryltransferase [GGT] stable; aspartate– and alanine aminotrasferase [ASAT and ALAT] decreased resp. increased slightly in the COBRA group in the first 6♣weeks; data not shown).

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Figure 2 **Line graphs of group means over time: ESR, mean blood pressure, weight gain and selected chemistry tests**. The gray area is the "Null Zone", the area where the group means reside when there is no significant difference at the two-sided p of 0.05. The initial period is magnified to better depict the rapid changes in the first weeks. Each vertical grid line equals a 4-week period. The thick grid lines show important changes in treatment schedule: end of step-down prednisolone, start of tapering low dose prednisolone, start of methotrexate tapering.

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Figure 3 Line graphs of group means over time: hematology tests. Explanations, see Figure 2.

Discussion

The results of the intensive monitoring schedule in the COBRA trial first of all confirm that RA causes profound disturbances in many physiologic parameters. The documented changes in the trial are the sum of (rapid or slow) improvement in disease activity with reversal of the abnormalities and specific effects of the drugs employed. In the first 4–8♣weeks most changes

are highly likely caused by the prednisolone dosing scheme. The biphasic platelet response in the COBRA group suggest an acute effect of platelet mobilization caused by prednisolone, followed by the antirheumatic effect which reverses thrombocytosis due to RA. It is less likely that an antirheumatic effect is the cause of the initial rapid increase in hemoglobin: reversal of anemia takes longer. Combined with the increases in creatinine it might be that RA itself causes changes in the distribution of intravascular fluid (i.e. hemodilution) which is reversed by therapy.

The second observation is that in this relatively healthy population the monitoring schedule is fairly inefficient in detecting clinically relevant abnormalities. This is of course a well-known problem in the monitoring of antirheumatic therapy, and one that cannot be solved by observations from randomized trials. Both the selection of the patients and the relative rarity of severe adverse events make it difficult to extrapolate toxicity findings from trials to general practice. Nevertheless, most events that are amenable to detection by lab monitoring occurred in the initial phases of treatment. On the basis of the COBRA experience, we would now suggest a check of body weight, blood pressure and lab (hematology, creatinine, liver function tests; urine for glucose and protein, preferably 2♣hours after a meal) at 1 and 3♣weeks after the start of therapy. If these tests are normal, there is no necessity for further monitoring other than that advised for single DMARD therapy. It should be noted that recommendations for such monitoring is mostly based on expert opinion rather than evidence.

In conclusion, early aggressive therapy of RA with step-down glucocorticoids according to the COBRA schedule causes rapid and highly consistent changes in blood pressure, body weight and lab parameters, contrasting with slower changes in patients treated with SSZ monotherapy. These changes are most likely the result of reversal of RA effects combined with intrinsic effects of the drugs in the combination, especially glucocorticoids.

References

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