A long-term, observational cohort study on the safety of low-dose glucocorticoids in ankylosing spondylitis: adverse events and effects on bone mineral density, blood lipid and glucose levels and body mass index

Yu-Ping Zhang,1 Yao Gong,1,2 Qing Yu Zeng,1,2 Zhi-Duo Hou,1 Zheng-Yu Xiao1

INTRODUCTION

Glucocorticoids (GCs) were introduced for the treatment of rheumatic disease in the 1950s, and their dramatic effects inspired physicians and patients. However, as the side effects and toxicity of long-term treatment with GCs (usually at doses that were median or high rather than low) emerged, physicians gradually lost confidence in GCs. Interestingly, in the last decade, GCs were reassessed in low-dose form. A large number of studies have shown that adverse events (AEs) of low-dose GCs in rheumatoid arthritis are moderate as long as the dose is low.1 2 However, in another chronic inflammatory disease, ankylosing spondylitis (AS), related research on GCs is scarce. Concerns about side effects may be one of the reasons why low-dose GCs are not commonly used in AS.3 Therefore, assessment of the safety of low-dose GC treatment in AS is important so that physicians can weigh the benefits against...
the potential risks based on evidence when they prescribe this conventional antirheumatic drug.

In the late 1980s, low-dose GCs were used for treatment of several patients with AS who were refractory to non-steroidal anti-inflammatory drugs (NSAIDs) in our clinic, and the results were satisfactory. Therefore, since the 1990s, low-dose GCs have been used more widely in AS, depending on the disease activity of patients. In our clinic, low-dose GCs were used in a large number of patients with AS with a long period of follow-up. Therefore, we performed a retrospective, observational cohort study to determine the safety of low-dose GCs in patients with AS.

**PATIENTS AND METHODS**

**Patients**

Our rheumatology department was established in 1983, and is one of the earliest specialised departments for rheumatic disease in China. Over the past 30 years, more than 2000 patients with AS were treated and followed up in our clinic. This study included patients who fulfilled the modified New York criterion, and were followed up for at least 6 months in the Rheumatology Outpatient Department of the First Affiliated Hospital of Shantou University Medical College from 1983 to 2012. Owing to the known AEs of lengthy GC therapy, the following exclusion criteria were applied: a previous history or current complications of active gastrointestinal problems, hypertension, psychiatric or mental problems, diabetes mellitus, tuberculosis and hepatitis. Demographics and patients' characteristics, including age, sex, duration of disease, duration of follow-up (for GC users, this started from the time of initiating low-dose GCs), height, weight, human leucocyte antigen (HLA) B27, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) levels at baseline, and data reflecting disease severity, such as the level of sacroiliac joint (SIJ) grading, and osteophytes in radiography of the spine were collected. Finally, 830 patients were included in this study. Among them, 188 patients were first-time visitors to our department during 1983–1999, and 642 patients during 2000–2012. At the time of analysis, follow-up data until June 2014 were available. The patients provided informed written consent for the use of their data. The data were anonymously analysed.

**Treatment, patient follow-up and AEs monitoring**

Low-dose GC users took 10 mg prednisone or 8 mg methylprednisolone tablets at 8:00, and a dose of NSAIDs (usually 90 mg acemetacin, 50 mg indomethacin or 7.5 mg meloxicam) before bedtime. Non-GC users only took a dose of NSAIDs before bedtime. Information regarding the dose of GC and duration of exposure was collected and categorised by cumulative duration of GC therapy as follows: no GC exposure (never took GCs), <6 months, 6 months to 2 years and ≥2 years. All patients were treated with conventional disease-modifying antirheumatic drugs, single or combined, depending on the disease activity. Conventional disease modifying anti-rheumatic drugs (DMARDs) that are used by rheumatologists in our department include sulfasalazine, methotrexate, azathioprine, thalidomide and some extracts of Chinese herbs, including *Tripterygium wilfordii* Hook F and total glucosides of paenly. All the patients took oral calcium and vitamin D concurrently, unless there was a specific contraindication.

In our clinic, all the patients were followed up every 1–3 months once the diagnosis was made and treatment strategies were decided. Physicians inquired about medication compliance and AEs, assessed disease activity at every visit, and all AEs were required to be recorded in the medical records. Routine blood examination, liver and renal functions and ESR and CRP levels were required to be tested at intervals of 1 month to half a year. BMD, blood lipid and glucose levels and BMI were required to be measured at intervals of 1 year. The DXA (dual energy X-ray absorptiometry) scanner was introduced to our hospital in 2005; BMD was not tested prior to that year. There were five to six doctors who regularly worked at our outpatient department. They followed the routines for each patient’s follow-up, and the decision whether to do a test or not were based on opinions of rheumatologists and the willingness of the patients.

**Assessment of AEs**

**Definition:** An adverse drug reaction was defined according to WHO definition, which refers to any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy.

By systematically reviewing clinical records, we investigated eight categories of AEs, which may be related to GCs, and were recommended to be monitored under low-dose GC treatment by the European League Against Rheumatism (EULAR): (1) cardiovascular system: hypertension, ischaemic cardiovascular disease; (2) serious infections: only infections that required hospitalisation or were life-threatening were counted because mild infections such as uncomplicated lower urinary tract and upper airway infections may be missed by the patients or may not be accurately assessed and/or recorded by the rheumatologist during the visit; (3) gastrointestinal system: peptic ulcer disease (confirmed by gastroscopy examination); (4) mood disturbances, sleep disorder; (5) endocrine and metabolic system: diabetes, body weight gain and fat redistribution; (6) dermatological system: acne, hirsutism, alopecia, bruisingibility and cutaneous infection; (7) musculoskeletal system: fragility fracture and (8) ophthalmological system: cataract. All the comorbidities were confirmed by the physician.

Furthermore, to assess the effects of low-dose GC treatment on bone mineral density (BMD), blood lipid and glucose levels and body mass index (BMI), we analysed related data and compared them between the two groups. By reviewing clinical data, we collected original
BMD data of 317 patients, fasting glucose levels of 335 patients, blood lipid levels of 190 patients and the BMI of 367 patients after treatment (the latest results for those who underwent more than one test were analysed). BMD was measured using a DXA scanner (DXA, DMS Lessos, France) in our hospital at the lumbar spine, the hip and the non-dominant forearm. For patients under the age of 50, ‘below the expected range for age’ was defined as a Z-score <-2.0 at more than one of the aforementioned sites. For patients aged 50 years or older, the WHO definitions of osteopenia and osteoporosis were used: osteopenia, -2.5<T-score <-1 SD, and osteoporosis, T-score<-2.5 SD. Considering that only 14 patients who had their BMD tested were older than 50 years, ‘BMD below the expected range for age’ and ‘osteoporosis’ are expressed conformably as ‘low BMD’ in this article. BMI is calculated as (weight in kilograms)/(height in metres^2). According to ‘the guidelines for prevention and control of overweight and obesity in Chinese adults’, obesity is defined as a BMI over 28 kg/m^2, while overweight is defined as a BMI between 24.0 and 27.9 kg/m^2. For teenagers under the age of 18, criteria with respect to their age are used. Dyslipidaemia is defined as the value exceeding these normal ranges (mmol/L): cholesterol (CHOL) 3.10–6.00; triglycerides (TRIG) 0.45–1.6; high-density lipoprotein (HDL) 0.8–2.35; low-density lipoprotein (LDL) 1.68–4.5. Hyperglycaemia is defined as a fasting blood glucose of at least 6.1 mmol/L. All blood tests were analysed by a single laboratory in our hospital.

Statistical analysis
All the data were analysed using SPSS software V.20.0 for Windows. Continuous data are presented as mean±SD, and categorical data are presented as numbers (n) or proportions (%). Baseline differences in patients’ characteristics between groups were analysed by the χ^2 test for categorical data or the Mann-Whitney U test for continuous data. The cumulative incidence rate and rate per 1000 patient-years of follow-up (duration of follow-up (years)× number of patients) were reported for GC-related AEs. For incidents that may occur repeatedly, such as cutaneous infection, only the first incident was included in the analysis of cumulative incidence, and only the first incident that occurred in 1 year was included in the analysis of the rate per 1000 patient-years of follow-up. The effects of low-dose GCs on BMD, blood lipid and glucose levels and BMI were modelled using multiple logistic regression analysis, controlling for potential confounding factors when appropriate. p Values less than 0.05 were considered statistically significant.

RESULTS
Characteristics in different subgroups
The study comprised 830 patients with a mean age of 28±10 years (range 10–62 years). The mean duration of disease was 6.5±6.0 years (range 0.25–40 years), and the HLA-B27-positive rate was 88.5%. The mean follow-up duration was 2.2±1.9 years (median 1.6 years; range 0.5–15 years). The overall follow-up was 1801 patient-years. Among them, 217 (26.1%) patients were followed up for more than 3 years.

Characteristics in different subgroups are shown in table 1. A total of 555 (66.9%) patients were treated with low-dose GCs, and the median cumulative duration of GC therapy was 1.3 years (range 0.1–8.5 years). Among them, 319 (57.5%) patients took low-dose GCs for more than 1 year, and 98 (17.7%) patients took them for more than 3 years. The median cumulative dose of GCs was 3.7 g (range 0.13–29 g). The other 275 patients were non-GC users, and they showed no differences from GC users regarding age, sex, disease duration or HLA-B27-positive rate. However, more patients in the GC group reached the SIJ-IV grading level at baseline, and the ESR and CRP levels at baseline were higher compared with the non-GC group. The mean duration of follow-up in the GC group was 2.4±2.1 years, which was significantly longer than that in the non-GC group (1.6±1.3 years, p=0.000). The overall follow-up of GC users was longer than that of non-GC users (1349 vs 452 patient-years).

AEs under low-dose GC treatment
The number of GC-related AEs was limited (table 2). Dermatological incidents, including acne, bruising and cutaneous infections, were the most common AEs, with a cumulative incidence rate of 5.4% (22.2 events per 1000 patient-years), followed by a puffy and rounded face, complaint of obvious weight gain and serious infections. The cumulative incidence rates of all the other

| Table 1 Characteristics of the different subgroups |
|------------------------------------------------|
|               | GC group | Non-GC group | p Value |
|----|---------|------------|---------|
| Number of cases | 555      | 275        |         |
| Age, mean±SD, years | 28±9     | 28±10      | 0.420   |
| Disease duration, mean±SD, years | 6.7±5.9  | 6.2±6.1    | 0.085   |
| HLA-B27 positive, n (%) | 393 (88.5) | 152 (88.4) | 0.961   |
| Male sex, n (%) | 242 (88) | 480 (86.5) | 0.542   |
| SIJ grade IV, n (%) | 58 (21.1) | 165 (29.7) | 0.008   |
| Spinal osteophytes, n (%) | 79 (30.6) | 179 (34.4) | 0.289   |
| ESR at baseline, mm/1 h* | 40±28  | 30±25      | 0.000   |
| CRP at baseline, mg/L* | 25.8±26.5 | 20.5±26.7 | 0.002   |
| Duration of follow-up, mean±SD, years | 2.4±2.1 | 1.6±1.3    | 0.000   |
| Duration of GC therapy, mean±SD, years | 1.7±1.6 |           |         |

*Some data were missing in these items at baseline: 214 cases of HLA-B27, 52 cases of spinal osteophytes, 80 cases of ESR, 178 cases of CRP.
The median cumulative duration of GC therapy by the time of AEs was less than 1 year, except for peptic ulcer disease. The mean age of patients with hypertension was 45±6 years, which is much higher than the average value of the population, with a median cumulative duration of GC therapy of 43 days (range 13–90 days). One patient in the GC group was diagnosed with diabetes at the age of 35 years, with a cumulative duration of GC therapy of 210 days. No cardiovascular events were reported in any of the patients who were followed up. In the non-GC group, no complications of diabetes, symptoms of weight gain, a puffy and rounded face, acne or bruisability were reported. The non-GC group showed a comparable incidence rate for the other types of AEs, except for dermatological AEs, which was significantly lower than that of the GC group (p=0.003; table 2).

### Multivariate analysis

The associations between GC exposure and the frequency of low BMD, overweight, obesity, hyperglycaemia and dyslipidaemia were assessed using a logistic regression model. Confounding factors (independent variables) for low BMD included age, male sex, BMI, ESR at baseline, GC groups (GC users or non-GC users), cumulative duration of GC therapy and spinal osteophytes. Confounding factors for overweight and obesity included age, GC groups and cumulative duration of GC therapy. Confounding factors for hyperglycaemia, and dyslipidaemia included age, BMI, ESR at baseline, GC groups and cumulative duration of GC therapy.

In multivariate analysis, GC groups and the duration of GC therapy were not associated with the frequency of low BMD, overweight, obesity, hyperglycaemia or dyslipidaemia. Low BMD was associated with male sex (OR 7.546, 95% CI 1.626 to 35.011), BMI (OR 0.695, 95% CI 0.606 to 0.797) and spinal osteophytes (OR 2.520, 95% CI 1.115 to 5.697). Overweight was associated with age (OR 1.064, 95% CI 1.038 to 1.091).
in some observational studies on older patients, such as those with rheumatoid arthritis and polymyalgia rheumatica, the incidence rate of GC-related AEs was usually much higher than that in our study, and it was associated with duration of GC exposure, especially osteoporosis, fragility fractures and hypertension.\textsuperscript{10–12} A relatively young age may be one of the reasons why comorbidity of hypertension, diabetes and cardiovascular events are scarce. A young population usually has less concurrent disorders, such as diabetes and hypertension, than an old population, and a longer duration of follow-up might be needed. However, similar levels of blood glucose and lipids and BMI between GC users and non-GC users in our study suggest that low-dose GCs do not have an adverse effect on the aforementioned events in the long term in patients with AS.

Another unique feature of this study is that we directly compared BMD, blood lipid and glucose levels and BMI in a large number of patients to evaluate the effect of low-dose GC on AS. Bone loss is assumed to be a common AE of GCs.\textsuperscript{13} In our study, in the GC group, even the number of long-term users with low BMD was similar to that in the non-GC group. Patients with AS have a high prevalence of low BMD due to the inflammatory nature of the disease.\textsuperscript{14,15} This study showed that low-dose GCs did not have an adverse effect on BMD in AS. Similarly, some studies on the BMD of patients with rheumatoid arthritis also indicated that low-dose GC treatment does not lead to bone loss, and may even improve BMD by controlling the disease activity.\textsuperscript{16,17} In this study, GC exposure was not associated with the frequency of hyperglycaemia, dyslipidaemia and obesity. Patients with AS have a higher risk of metabolic syndrome and cardiovascular events due to an elevated inflammation level.\textsuperscript{18,19} Our finding of decreased abnormal levels of cholesterol, triglycerides and low-density lipoprotein as the cumulative time of GCs increased may be related to control of inflammation. Similarly, some studies did not show any association between GC use and abnormal blood lipid levels or the presence of metabolic syndrome in rheumatic disease.\textsuperscript{20,21} In general, GCs have a complicated effect on blood lipid and glucose levels and BMD in inflammatory rheumatic disease. Control of inflammation by GCs improves the abnormal metabolism of blood lipid and glucose levels and an abnormal course of bone remodelling. However, GCs can also aggravate these outcomes. Low-dose GCs may be a good balance point between these two opposite outcomes. Low-dose GCs were not recommended in AS in the Assessment of SpondyloArthritis International Society (ASAS)/EULAR management recommendation due to lack of evidence.\textsuperscript{22} However, to the best of our knowledge, traditional antirheumatic drugs, including low-dose GCs, still play a role in the treatment of AS and need to be reassessed in more studies, especially on patients at the early stage of disease. We were not in a minority in using low-dose GCs in the treatment of AS in China regarding its cost-effectiveness. Even in the European countries, related articles reported that from baseline data of early studies with antitumour necrosis factor agents and other agents, 10–25% of patients with AS are treated more or less continuously with GCs, and the German collaborative arthritis

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**Table 3** Comparison of the proportion of patients with low BMD, abnormal blood lipid and blood glucose levels, overweight and obesity between GC users and non-GC users

|                         | RR value (GC users vs non-GC users) | Non-GC users | GC users | Grouping by duration of GC therapy | GCs<0.5 years | GCs 0.5–2 years | GCs >2 years |
|-------------------------|-------------------------------------|-------------|----------|-----------------------------------|---------------|----------------|--------------|
| BMD                     |                                     |             |          |                                   |               |                |              |
| Number of cases         |                                     | 111         | 206      | 26                                | 4 (15.4)      | 24 (27.0)     | 21 (23.1)    |
| Low BMD, n (%)          | 1.15 (0.74–1.78)                    | 23 (20.7)   | 49 (23.8) | 4                                  | 26            | 89             | 91           |
| Blood lipids            |                                     |             |          |                                   |               |                |              |
| Number of cases         |                                     | 61          | 129      | 22                                | 22            | 68             | 39           |
| Elevated CHOL, n (%)    | 2.84 (0.66–12.35)                   | 2 (3.3)     | 12 (9.3) | 2                                  | 2 (9.1)       | 9 (13.2)      | 1 (2.6)      |
| Elevated TG, n (%)      | 0.68 (0.31–1.51)                    | 9 (14.8)    | 13 (10.1)| 2                                  | 2 (9.1)       | 8 (11.8)      | 3 (7.7)      |
| Decreased HDL, n (%)    | 0.64 (0.11–3.75)                    | 2 (3.6)     | 3 (2.3)  | 0                                  | 0             | 2 (3.0)       | 1 (2.6)      |
| Elevated LDL, n (%)     | 2.18 (0.26–18.18)                   | 1 (2.5)     | 4 (4.1)  | 1                                  | 1 (4.5)       | 3 (4.6)       | 1 (2.6)      |
| Blood glucose           |                                     |             |          |                                   |               |                |              |
| Number of cases         |                                     | 136         | 199      | 54                                | 92            | 52             | 52           |
| Elevated glucose, n (%) | 0.273 (0.05–1.39)                   | 5 (3.7)     | 2 (1.0)  | 0                                  | 2 (2.2)       | 0              |              |
| BMI                     |                                     |             |          |                                   |               |                |              |
| Number of cases         |                                     | 137         | 230      | 31                                | 119           | 80             |              |
| Overweight, n (%)       | 0.74 (0.49–1.11)                    | 33 (24.1)   | 41 (17.8)| 5 (16.1)                          | 20 (16.8)     | 16 (20.0)     |              |
| Obesity, n (%)          | 1.64 (0.53–5.05)                    | 4 (2.9)     | 11 (4.8) | 0                                  | 8 (6.7)       | 3 (3.8)       |              |

All the p values between the GC subgroup (GCs <0.5, 0.5–2 or >2 years) and non-GC users were over 0.05.

*Out of the patients who had their blood lipids tested after treatment, six cases missed the data of HDL, and eight cases missed the data of LDL.

BMD, bone mineral density; BMI, body mass index; CHOL, cholesterol; GC, glucocorticoid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RR, relative risk; TG, triglyceride.
centre’s database registered a current treatment with low-dose GC therapy in 15.6% of the patients with AS.\textsuperscript{23}
Actually, there is no reasonable doubt that GCs could improve the symptoms of AS, considering its greater anti-inflammatory properties than NSAIDs. However, there were no clinical studies evaluating the effectiveness of low-dose corticosteroids in AS. The comment following the ASAS/EULAR management recommendation about GCs was “there have been no new studies, and the available literature is still scarce.”\textsuperscript{22} Our study may be the first attempt to reassess the value of low-dose GCs to patients with AS, as concerns about side effects may be one of the reasons why low-dose GCs are not commonly used in AS.\textsuperscript{3}

Our study could help physicians to weigh the benefits against the potential risks when they prescribe this conventional antirheumatic drug in clinical practice.

As a retrospective cohort study, there were inevitably some limitations. First, confounding factors were the main limitation for this observational design. We have adjusted for potential confounding factors by a regression model, but the adjustment itself had limitations due to the retrospective nature of this study. Second, as not all the patients had their BMD, BMI or blood glucose tested after treatment, the missing data may be a bias. However, as an original clinical database with consecutive patients, some data may be kind of randomly missed. Third, adverse events of GCs, like cardiovascular events and diabetes, were usually chronic incidents during long-term treatment, and therefore the median follow-up duration of 1.6 years may not be sufficiently long enough to evaluate the long-term safety. We are looking forward to more well-designed studies to confirm our results.

In conclusion, our study shows that AEs during long-term treatment of low-dose GCs are limited. Low-dose GCs do not have an adverse effect on BMD, blood lipid and glucose levels, or BMI. In the young and mainly male population of patients with AS, low-dose GCs are relatively safe. Our findings may help physicians and rheumatologists to gain new insight into the traditional antirheumatic drugs that are GCs.

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