Concise Report

Low disease activity state with corticosteroid may not represent ‘true’ low disease activity state in patients with rheumatoid arthritis

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Objective. Corticosteroids constitute one of the most common treatments of RA. The purpose of this study is to investigate whether long-term corticosteroid use suppresses the progression of disability in RA patients with low disease activity state.

Methods. Data collected from a large observational cohort of RA patients at our institution were analysed for 214 RA patients whose disease activity score (DAS) 28 and HAQ were available consecutively from October 2000 to October 2004. All 214 patients had average DAS 28 3.2, meaning only those who had well-controlled RA disease activity were chosen as subjects. The subjects were divided into steroid users who received continuous corticosteroids every month and non-steroid users who did not receive consecutive corticosteroids continuously every month.

Results. Fifty-five patients (25.7%) were corticosteroid users and 159 (74.3%) were non-users. Average prednisolone for the former group was 4.2 mg/day. No significant differences were observed among baseline variables and RA disease activity variables. However, for steroid users, HAQ progressively worsened with time and for non-steroid users, HAQ progressively improved.

Conclusions. Although DAS 28 and other variables may suggest well-controlled RA disease activity, functional capacity of patients on low-dose corticosteroids deteriorated. Thus, low disease activity state with corticosteroid may not represent the ‘true’ low disease activity state. Along with the achievement of a low disease activity state, long-term efficacy, prognosis, and the quality of remission need to be also considered in the tight control of RA activity.

KEY WORDS: RA, Corticosteroids, Disease activity score 28, HAQ, Epidemiology.

Introduction

Corticosteroids constitute one of the most common treatments of RA. Studies show that of the newly diagnosed RA patients, 20–40% use steroids, and when looking at the RA patient population as a whole, >75% will have used steroids at least once during the course of the disease [1–2]. A recent report even states that 37% of RA patients regularly followed by rheumatologists receive no DMARDs, but oral steroids alone [3].

Although commonly used in the treatment of RA, the high therapeutic potency of corticosteroids on one hand and their potential to cause adverse effects on the other has been debated. Undoubtedly, corticosteroids at low doses provide short-term relief from symptoms of RA whether used for a brief time, intermediate or longer use [4]. However, no reports provide enough evidence to state a definite stance on the use of corticosteroids. Recently, a number of studies have supported the use of low-dose corticosteroids in addition with DMARDS, which significantly reduce radiographic progression of RA [5–11]. These studies show that short-term low-dose steroids used in early RA slow down joint destruction, but there are other studies that claim steroids do not have this kind of benefit at all [12–14].

In addition, corticosteroids are known for their adverse effects and short-, intermediate- and long-term toxicities have been well-documented. Even at low dose, long-term use may be associated with severe outcomes [15, 16].

Further studies are necessary to construct enough evidence to assess the use of corticosteroids in RA patients and to address the benefits and risks of the treatment. The purpose of this study is to investigate whether long-term corticosteroid use suppresses the progression of disability in RA patients with low disease activity state.

Patients and methods

Cohort database

A case-control study was conducted using the following cohort database. The patient cohort of our investigation is based on a large non-interventional observational cohort study [Institute of Rheumatology RA, (IORRA) cohort] and approved by the university’s ethics committee. Since October 2000, all RA patients meeting the 1987 ACR criteria for RA, visiting the outpatient clinic of the Institute of Rheumatology, Tokyo Women’s Medical University (Tokyo, Japan) are asked to answer a validated questionnaire every 6 months. The questionnaires assess variables such as disability level, assessment of pain, global assessment of disease activity, use of medication, adverse events, health care utilization and satisfaction of care [17]. Further database includes physician’s assessments, patient-reported data and laboratory data. Approximately 5000 RA patients are included per study, and a response rate of >98% is achieved each time. The near-perfect response allows for practical and high quality epidemiological data on rheumatic diseases in Japan.

Selection of patients

Data and information collected bi-annually from October 2000 through October 2004 were used for this study. Patients were selected under the following criteria: (i) data available for four consecutive years, (ii) average DAS 28 during the 4 yrs ≤ 3.2, meaning only patients with controlled disease activity were selected.

Case patients are defined as taking any daily dosage of oral corticosteroids continually between October 2000 and October 2004. Control subjects are identified as all other RA patients. Patients who use corticosteroids, but not daily, are considered non-steroid users.

A total of 214 RA patients (74.8% females, average age 55.6 ± 11.3 yrs, disease duration 8.4 ± 8.3 yrs) were selected on the basis of the patient selection criteria. Of the 214 patients, 55 were consecutive corticosteroid users and 159 were non-corticosteroid users.
The following criteria were collected and analysed: DAS 28, HAQ, tender joint count (TJC) 28, swollen joint count (SJC) 28, patient’s assessment of pain on a visual analogue scale [patient’s pain VAS (pVAS)], patient’s global assessment of disease activity [patient’s global VAS (gVAS)], physician’s global assessment of disease activity [physician’s global VAS (dVAS)], CRP, ESR, RF positivity, various DMARD treatment (more than a month of treatment), average weekly MTX dose and average daily prednisolone (PSL) dose.

**Statistical analysis**

Continuous variables are expressed as the mean, s.d, median, 25 and 75% values. Discrete variables are described with percentages. Primary end points were set at HAQ slopes for each individual patient, in which each patient HAQ slope was calculated using a linear regression analysis for all HAQ data available for that particular individual. Logistic regression was calculated using a linear regression analysis for all HAQ data and 75% values. Discrete variables are described with percentage. The Mann–Whitney U-test was used for the comparison of the average HAQ slopes for applied for the analysis of the HAQ slope, and the Mann–Whitney U-test was used for the comparison of the average HAQ slopes for the two groups. Level of significance was set at 5% and two-sided P-values are given.

**Results**

Baseline patient characteristics are shown in Table 1. Consecutive steroid users made up 25.7%, while those that did not use steroids consecutively (the non-steroid users) made up 74.3%. The baseline DAS 28 was 3.22 ± 0.75 and 3.23 ± 0.93 for steroid users and non-users, respectively. HAQ for steroid users was 0.25 [0, 0.75] and 0.25 [0, 0.625] for the non-users. No significant differences were observed in any of the baseline components, including age, number of females, disease duration, present MTX use and MTX dosage (data not shown). The average steroid use for the steroid users was 4.2 mg/day. Biologics were not used by any of the patients in either group. It should be noted here that infliximab and etanercept, the only two approved biologics at the present time in Japan, were not approved until 2003 and 2005, respectively, and therefore, none of the patients included in our study were treated with biologics at the time.

Table 2 shows the coefficients obtained through a multiple logistic regression. By adjusting the effects of other confounding factors, it was found that only HAQ slope showed significant differences between the two groups (P = 0.02).

**Discussion**

Corticosteroids are powerful anti-inflammatory agents that have been extensively used in RA treatment since the 1940s. It is now generally accepted that early diagnosis and early suppression of inflammation are important requisites for a favourable outcome of RA and because high daily doses of corticosteroids over long-term have considerable toxicity, alternative approaches, such as short-term high dose, long-term low dose, long-term low dose corticosteroids with conventional DMARDs have been explored. The critical question is whether the use of corticosteroids can reduce the progression of joint destruction and sustain low disease while preventing or minimizing the exhibition of drug toxicity.

Our present study indicated that although clinical manifestations of RA patients represented by DAS 28 may suggest controlled disease activity, when looking at overall long-term prognosis in terms of HAQ, those patients utilizing consecutive corticosteroids (at low dose) demonstrated worsening HAQ scores, indicating progression of disease, while those not using continuous corticosteroids showed an improvement of HAQ scores and disease progression.

There are several factors that could have influenced our results. First, our study was a retrospective case–control study. A limitation to this kind of study is that it does not directly measure the risk, and it is susceptible to bias. Second, corticosteroid use, the key factor to this study, was reported by the patients themselves. This study was carried out under the assumption that the use of the drug was correctly and truthfully reported. Other factors that may affect the results are adverse events of corticosteroids that could worsen HAQ or the mere fact that patients with worse symptoms were given more PSL. Although these reasons seem minimal or unlikely given the fact that if adverse events did occur they would be detected and measures would be taken, and baseline disease activity
parameters, such as DAS 28 and HAQ, for users and non-users were very similar (Table 1).

Our study shows improvement of clinical symptoms and DAS 28 for both long-term corticosteroid users and non-steroid users, but HAQ worsened with the former. We can hypothesize from our results that while corticosteroids exhibit anti-inflammatory effects, it does not prevent the progression of joint destruction and bone erosion. For example, serum MMP-3, which is responsible for degradation many components of the cartilage and bone extra-cellular matrix and activating pro-MMPs into their active forms, has been shown to increase with oral corticosteroid therapy and decrease with biologics and MTX [18–20]. This could lead to the more harmful nature of the use of corticosteroids. However, since there are reports of corticosteroids retarding radiographic progression in early RA, differences in responses may exist according to the stage of the disease [5–11]. Further examination of disease stage and the effects of corticosteroids need to be considered.

The strong immunosuppressive and anti-inflammatory properties of corticosteroids make them indispensable for the treatment of acute and chronic inflammatory diseases, especially rheumatic diseases such as RA. Our study suggests that low disease activity state with the use of corticosteroid may not represent the ‘true’ low disease activity state. Along with the achievement of a low disease activity state, long-term efficacy, prognosis and the quality of remission need to be also considered in the tight control of RA activity, and it is crucial that further evaluations be made concerning the use of corticosteroid treatment.

**Rheumatology key messages**

- Both long-term and short-term effects must be considered.
- Use of corticosteroids does not necessarily slow disease progression even with low disease activity.

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