Nonsteroidal Antiinflammatory Drug Withdrawal in Patients with Stable Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the effect of nonsteroidal antiinflammatory drug (NSAID) withdrawal on blood pressure (BP), 44-joint Disease Activity Score (DAS44), and functional assessments in patients with stable rheumatoid arthritis (RA).

Methods. NSAID was withdrawn from 30 patients with stable RA (DAS44 ≤ 2.8). Other prescribed medication continued. Clinical and laboratory measures were taken at baseline, 6 weeks, and 12 weeks.

Results. No participants required NSAID reintroduction during the study period. Significant improvement in systolic BP was noted: maximal median reduction was 7 mm Hg (baseline to 12 weeks). There was no significant deterioration in DAS44 or function. Eleven participants required additional intervention.

Conclusion. NSAID withdrawal resulted in improvement in BP without loss of disease control. (First Release July 1 2011; J Rheumatol 2011;38:2150–2; doi:10.3899/jrheum.101162)

Key Indexing Terms:
BLOOD PRESSURE
NONSTEROIDAL ANTIINFLAMMATORY AGENTS
RHEUMATOID ARTHRITIS
RISK FACTORS

The morbidity and mortality associated with rheumatoid arthritis (RA) is well documented; life span is reduced by 3–18 years[1]. This excess mortality is due to cardiovascular (CV) events, secondary to atheromatous vascular disease. Inflammatory mechanisms are a key response in the initial endothelial damage and the subsequent progression of atheromatous plaques. General population estimates calculate that > 70% of those with atheroma-related CV disease have ≥ 1 traditional Framingham risk factor[2].

Nonsteroidal antiinflammatory drugs (NSAID) are frequently prescribed to patients with RA. Most of these drugs raise blood pressure (BP) by about 5 mm Hg[3]. Accumulating evidence has implicated cyclooxygenase-2-specific and nonselective NSAID with an increase in acute myocardial infarctions[4,5]. In 2006, the American Heart Association advised that to minimize CV risk, anyone prescribed an NSAID should have the lowest dose administered for the shortest possible time[6].

Although clinical experience and expert opinion advise that NSAID should be withdrawn in patients with RA who have well controlled disease[7], there is no evidence that this improves the risk/benefit ratio associated with their use. Our aim with this study was to evaluate the feasibility of NSAID withdrawal and to identify potential benefits from withdrawal in patients with stable RA, focusing on disease activity and BP control.

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MATERIALS AND METHODS

Local ethics committee approval was given. Study enrollment is documented in Figure 1 and inclusion and exclusion criteria in Table 1. Thirty patients were recruited and gave written informed consent. As this was an open-label observational feasibility study, no specific power calculations were performed. A sample size of 30 patients was considered large enough to provide helpful results but small enough to allow rapid followup.

Patients were asked to stop prescribed NSAID abruptly, without tapering the dose. Disease-modifying antirheumatic drug (DMARD) therapy was continued. General practitioners were asked not to prescribe NSAID for the duration of our study and patients were requested not to self-administer over-the-counter NSAID, as explained in the patient information sheet. Use of acetaminophen or codeine-containing compound analgesia was allowed. Patients were encouraged to make telephone contact if further advice was required between scheduled visits. If appropriate, steroid injection or dose escalation of DMARD could be arranged (as per study regimen).

These clinical features were documented at baseline, 6 weeks, and 12 weeks: tender and swollen joint count, erythrocyte sedimentation rate, patient global assessment of disease activity (visual analog scale, VAS), DAS44, pain score (VAS), and Short Form-12 v2 Health Survey (SF-12) functional assessment[8].

These CV risk factors were documented: smoking habits, systolic and diastolic BP, total and high-density lipoprotein cholesterol, triglycerides, and body mass index (BMI). A British Hypertension Society (BHS)-approved digital sphygmomanometer was used throughout the study to record BP. BHS guidelines were followed for BP recordings[9].

SPSS version 15.0 software was used for statistical analysis.

RESULTS

Baseline demographic and clinical characteristics are documented in Table 2. Forty-seven percent of participants were

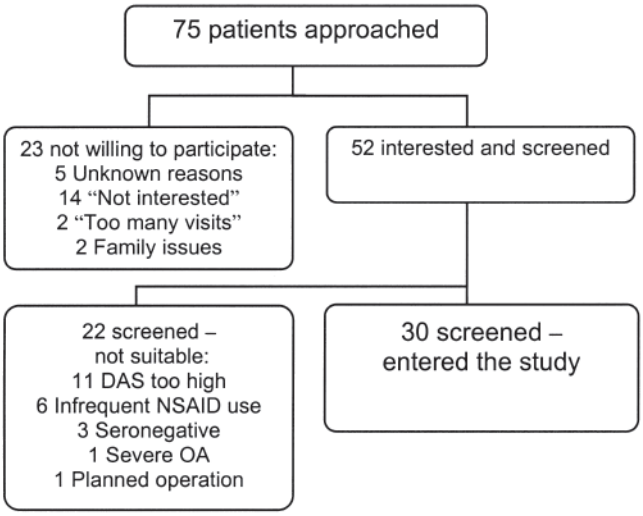

Figure 1. Selection of participants for the study. DAS: Disease Activity Score; NSAID: nonsteroidal antiinflammatory drug; OA: osteoarthritis.

Table 1. Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Rheumatoid factor seropositivity	Concurrent diagnoses of
DAS44 ≤ 2.8	Fibromyalgia
Stable dose DMARD for ≥ 1 month	Severe osteoarthritis
Prednisolone ≤ 10 mg/day (if taken)	Dysmenorrhea
NSAID used on ≥ 25/30 days per month	Planned operative intervention

DAS44: 44-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drug; NSAID: nonsteroidal antiinflammatory drug.

ever-smokers and 20% were current smokers. One-third were classified as obese (BMI > 30 kg/m^2). One patient was prescribed low-dose prednisolone and 3 patients antitumor necrosis factor therapy at study outset. All 30 patients completed the 12-week study without reintroduction of NSAID.

A significant reduction in systolic BP was observed with NSAID withdrawal at Week 6 (median reduction of 5 mm Hg; $p = 0.025$) and Week 12 (median reduction 7 mm Hg compared with baseline; $p = 0.037$; Table 2). No significant change in diastolic BP was recorded. Of the patients prescribed antihypertensives (40%), none had their regimen altered during the intervention period. Changes in systolic BP over the course of study participation for each patient are documented in Figure 2.

There was no overall change in DAS44. A significant increase was seen in patient global assessment and pain score from baseline to 6 weeks ($p = 0.009$ and $p < 0.0001$, respectively), but there was a significant reduction in both measures back to near baseline values by 12 weeks. At baseline, the median SF-12 physical score was < 50, representing a below-average physical function. There was a nonsignificant trend in reduction in physical component score from baseline to 6 weeks. By 12 weeks there was a significant improvement in this measure.

A total of 13 steroid injections were given to 11 study participants over the entire intervention period. Only 1 participant required increased DMARD dose.

DISCUSSION

We have demonstrated that NSAID withdrawal is feasible in this group, with minimal additional intervention. No significant deterioration was noted in self-assessed function, as measured by SF-12.

Hypertension is one of the most important Framingham risk factors contributing to overall CV risk. It was therefore relevant that we found NSAID withdrawal resulted in a median 7 mm Hg fall in systolic BP at 12 weeks compared to baseline. A 3 mm Hg rise in systolic BP increases the occurrence of congestive cardiac failure by 10%–20%, the risk of stroke by 15%–20%, and angina by 12%[10]. A larger randomized controlled study may go some way to explain the cause of the improved BP, which at the moment remains hypothetical. One possibility is that the patients may have become acquainted with and relaxed within the study environment, with reduction in BP ensuing. We do not know whether BP changes are limited to certain levels. The early increase in pain and patient global scores may have been minimized by a tapered dose reduction of NSAID.

We acknowledge the limitations of our open-label, nonrandomized study, with small numbers and short duration. Data regarding steroid injection requirements pre-NSAID withdrawal may have aided comparison. Ours was a preliminary study intended to inform future work. We proposed to study patients with RA with a low to moderate DAS, but the local ethics committee advocated restricting the study to patients with low DAS. This is to our knowledge the first supportive evidence to guide the limitation of NSAID use in stable RA. We demonstrate that it is possible to withdraw NSAID in patients with a low DAS without adversely affecting their quality of life or disease control and without the need for significant additional input. We have also demonstrated additional benefits on systolic BP control that has important implications for reducing CV risk. Future studies of CV risk in RA should take into account the influence of NSAID-induced hypertension.

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Table 2. Demographic and clinical variables at baseline, 6 weeks, and 12 weeks. Data are median (range) unless otherwise specified.

Variables	Baseline	Week 6	Week 12
Age, yrs	59 (33–73)	—	—
Disease duration, yrs	11 (1–40)	—	—
Female sex, %	73	—	—
Total cholesterol, mmol/l	5.15 (3.4–7.4)	—	—
High-density lipoprotein, mmol/l	1.4 (0.8–32)	—	—
Triglycerides, mmol/l	1.05 (0.5–3.6)	—	—
Body mass index, kg/m^2	26.6 (22.04–44.74)	—	—
Systolic BP, mm Hg	141 (109–190)	136* (104–170)	134** (106–171)
Diastolic BP, mm Hg	87 (72–103)	85 (66–99)	84 (72–105)
DAS44	2.08 (0.26–2.79)	2.19 (0.65–5.08)	1.79 (0.76–2.95)
ESR, mm/1st h	5 (2–35)	8 (2–51)	7 (2–38)
Patient global assessment, VAS 100 mm	29 (4–61)	43*** (7–77)	25† (1–55)
Pain score, VAS 100 mm	20 (4–53)	37†† (7–72)	25$^{\#}$ (1–72)
SF-12 physical component	37.4 (24.5–56.6)	34.4 (24.5–55.1)	40.3 (31.6–56.7)
SF-12 mental component	54.4 (30.4–66.5)	54.0 (27.1–63.4)	54.5 (38.4–66.1)

Compared with baseline data (Wilcoxon matched-pairs signed-rank test): * p = 0.025 (improvement); ** p = 0.037 (improvement); *** p = 0.009 (deterioration); †† p < 0.0001 (deterioration). Compared with 6-week data (Wilcoxon matched-pairs signed-rank test): † p = 0.003 (improvement); $^{\#}$ p = 0.008 (improvement). BP: blood pressure; DAS44: 44-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; VAS: visual analog scale; SF-12: Medical Outcomes Study Short Form-12 Health Survey.

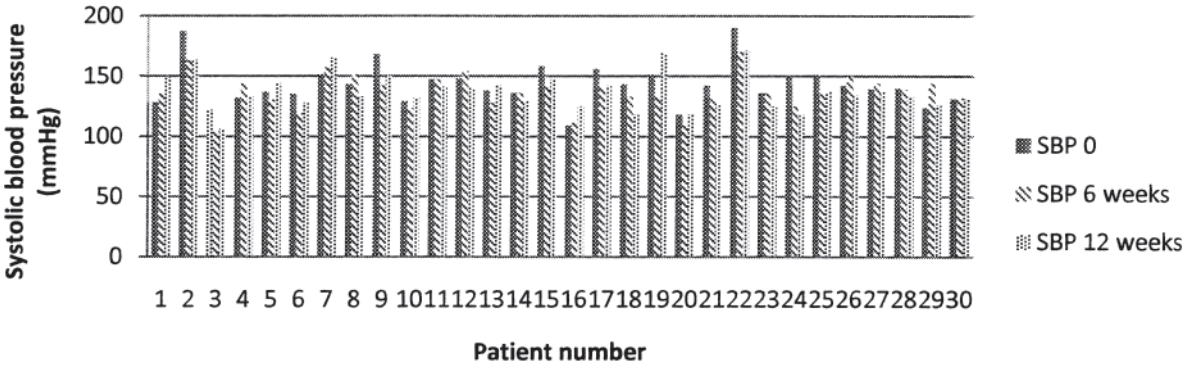

Figure 2. Systolic blood pressure (SBP) readings for individual patients at baseline, 6 weeks, and 12 weeks.

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