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Original article

Clinical relevance of C-reactive protein in ankylosing spondylitis and evaluation of the NSAIDs/coxibs' treatment effect on C-reactive protein

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Abstract

Objective. To evaluate the clinical relevance of CRP in AS and investigate the treatment effect of NSAIDs/coxibs on CRP.

Methods. Data of 851 patients with painful axial AS participating in two randomized controlled trials evaluating coxibs (celecoxib) and NSAIDs (naproxen/ketoprofen) were used. The clinical relevance of CRP in AS was studied: the number of patients with abnormal CRP at baseline was expressed as a percentage, and the correlation among CRP, patient (age and gender) and disease [Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI)] characteristics was investigated. The standardized response mean (SRM) over placebo was used to detect the treatment effect of NSAIDs/coxibs on CRP.

Results. The 851 enrolled patients (73% of whom were men) had an active disease, as assessed through functional impairment. Mean (S.D.) baseline CRP was 14 (19) (median 7.2) mg/l; 61% of patients had an increased CRP. The CRP levels were correlated positively with male sex, BASDAI and BASFI and negatively with age (multivariate analysis). There was a significant difference in the changes of CRP between placebo and NSAIDs/coxibs group ($P = 0.003$; SRM over placebo: 0.25). Such a treatment effect was of higher magnitude in the subgroup of patients with increased CRP and usually of lower magnitude than the treatment effect of other outcome variables such as BASDAI and BASFI.

Conclusions. Increased CRP was frequently observed in patients with painful axial AS and was correlated both with activity and functional severity of the disease. The treatment effect of NSAIDs/coxibs was relevant in the subgroup of patients with increased CRP at baseline.

Key words: Ankylosing spondylitis, C-reactive protein, Outcome measure, Treatment effect, NSAIDs/coxibs.

CLINICAL SCIENCE

Introduction

As a general overview, the outcome measures in rheumatic disorders can be categorized as follows:

(i) symptoms perceived by patients (e.g. pain, functional impairment and fatigue);
(ii) structure (e.g. joint destruction, joint space narrowing, sub-chondral bone erosions in RA and ossification in AS); and
(iii) inflammation (e.g. number of swollen joints in RA, MRI spinal/sacroiliac abnormalities in AS and increase in acute phase reactants in both diseases).

It is obvious that these three outcome measures are inter-related. For example, pain experienced by the patient can be related to an inflammatory episode of the disease or to structural deterioration of the disease. Most of the researchers consider that destruction is driven by inflammation. Therefore, 'inflammatory outcome measures' are viewed as surrogate markers of structural outcome measures. This statement has been fully validated in RA and suggested in AS [1]. The use of inflammatory markers such as CRP is recommended by the

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Assessment of SpondyloArthritis international Society (ASAS) and CRP is a component of the future ASAS-endorsed disease activity score (ASDAS score) [2]. Moreover, CRP is also considered as a surrogate marker of subsequent cardiovascular disease [3].

CRP should nevertheless fulfil the 'OMERACT filter' in order to be considered as a relevant outcome measurement in AS and in particular with the following characteristics: simplicity, reliability and validity [4, 5]. Simplicity is obvious because CRP measurement requires only a blood sample and is performed in daily practice. Reliability of CRP measurement has been shown as high in several studies [6–8]. Validity of CRP measurement is probably the most important and covers several concepts.

- External validity: this characteristic might be evaluated by the level of correlation between CRP and other outcome measures, reflecting the concept to be evaluated (e.g. activity and severity).
- Predictive validity: this characteristic requires a longitudinal study in order to evaluate the level of correlation between CRP at a single point of time *vs* a subsequent hard endpoint such as structural deterioration.
- Sensitivity to change/discriminant capacity requires the evaluation of changes over time, before and after an effective therapy and, if possible, to take into account the 'background noise' due to the natural history of the disease. Optimally, this characteristic should be evaluated in placebo-controlled randomized trials.
- Non-selective and cox-2-selective non-steroid drugs (NSAIDs/coxibs) are considered as the cornerstone therapy of AS. This recognition is mainly due to the symptomatic effect of these drugs and most clinicians consider these drugs as purely symptomatic without any effect on the domain 'inflammation' and subsequently as being without any disease-modifying effect. Currently, this notion should be revisited since a recent report suggested that a continuous daily intake of NSAIDs slowed down the structural progression of AS (evaluated on X-rays) over 2 years [9].

The objectives of the present study were to evaluate the clinical relevance of CRP and investigate the magnitude of the NSAIDs/coxibs treatment effect on this parameter, in patients with painful axial AS.

Patients and methods

We took the opportunity of having access to two databases of large randomized placebo-controlled trials (RCTs) conducted by Pfizer in this field (Study A [10] and Study B [11]).

Patients

In both studies, patients had a diagnosis of AS according to modified New York criteria [12], with axial involvement, with or without peripheral enthesopathy, without peripheral joint involvement. Pain intensity (0–100) at baseline had to be >50 and 40 mm in Studies A and B, respectively. A flare design was required in both studies (worsening of at least 30% in pain intensity) after a wash-out period of 14 days in Study A, and 2–14 days in Study B. In both trials, inclusion and exclusion criteria did not refer to a specific CRP level threshold. Patients participating in these two trials were included in the present study if the CRP levels were available at the baseline visit.

Treatments

Both trials were randomized placebo-controlled. Apart from the placebo, the study treatments were celecoxib 200 mg/day daily (QD) *vs* celecoxib 400 mg QD *vs* naproxen 500 mg twice daily (BID) and celecoxib 100 mg BID *vs* ketoprofen 100 mg BID in Studies A and B, respectively. Studies A and B were of 12 and 6 weeks' duration, respectively.

Outcome measures

The following patient characteristics were collected at baseline: age, sex and HLA B27 status (only in Study B for the last one). The following disease characteristics were collected at baseline and final visits: Bath AS Functional Index (BASFI), Bath AS Disease Activity Index (BASDAI), Patient's Global Assessment of Disease Activity (PGADA) and pain; BASDAI was collected only at the baseline in Study B. The disease duration was only available in Study B. CRP was measured at baseline and final visits in both studies.

Statistical analysis

Descriptive analysis of CRP at baseline. A descriptive analysis of CRP was conducted at baseline in all patients included in this study.

External validity of CRP. The level of correlation among CRP, patient characteristics (age, sex and B27 status) and disease characteristics (pain, BASDAI, BASFI and PGADA) was evaluated using three different techniques.

- The first one was univariate analyses (Spearman's rank correlation coefficient and Wilcoxon test).
- The second one was a multiple linear regression in which the CRP level defined the dependent variable and all the patient and disease characteristics selected by the univariate analysis ($P < 0.20$) defined the independent variables.
- The third one was a logistic regression in which a CRP >5 mg/l was the dependent variable, with similar thresholds as above for the independent variables.

Sensitivity to change and discriminant capacity. The sensitivity to change was assessed by calculating the standardized response mean (SRM: ratio of the mean changes over the S.D. of the changes) in the different treatment arms [13]. The 95% CI of each SRM was estimated using a bootstrap technique when possible. This analysis was conducted in patients completing the treatment period (completer population).

The discriminant capacity was assessed by calculating the SRM over placebo (i.e. the absolute value of 'SRM active minus SRM placebo'). It is usually admitted that a treatment effect can be considered as nil, mild, moderate and relevant for an observed value of <0.20, 0.20–0.40, 0.40–0.60 and >0.60, respectively [13]. Such sensitivity to change and discriminant capacity were calculated for different subgroups (e.g. pooled NSAIDs/coxibs groups, cox-2 selective *vs* NSAIDs and celecoxib 200 *vs* 400 mg). A *P*-value <0.05 was considered as significant in a two-tailed test.

In the pooled NSAIDs/coxibs *vs* placebo analysis, the CRP–SRM over placebo was calculated in different subgroups according to the baseline CRP (<5, 5–10, 10–15, 15–20 and >20 mg/l).

Finally, the CRP–SRM over placebo in the pooled NSAIDs/coxibs *vs* placebo analysis was compared with the SRM observed for other conventional outcome measures (BASDAI, BASFI, PGADA and pain SRMs).

Ethical committee. The two previously described RCTs were approved by an ethical committee.

Results

Patients—study course

A total of 857 patients were included (611 and 246 patients in Studies A and B, respectively). Eight hundred and fifty-one patients met the inclusion criteria for the present analysis (six were excluded because of unavailable CRP at baseline). Seven hundred and ninety-seven patients completed the treatment period (Fig. 1).

The main characteristics of the 851 patients are summarized in Table 1. Almost 73% were men; they had an active [pain (0–100): 70.9 (15.7), BASDAI (0–100): 56.0 (18.7)] and severe [BASFI (0–100): 49.3 (23.3)] disease. Of the 245 patients receiving a non-selective NSAID, 89 and 156 received ketoprofen and naproxen, respectively. Of the 375 patients receiving a cox-2-selective inhibitor, 214 and 161 received celecoxib 200 and 400 mg, respectively.

Descriptive analysis of CRP at baseline

CRP level ranged from 0 to 195 mg/l at baseline. Mean CRP was 14.0 (18.6) (median 7.2) mg/l; an increase in CRP over 5, 10, 15 and 20 mg/l was observed in 522 (61%), 328 (39%), 249 (29%) and 181 (21%) patients, respectively.

External validity of CRP

The univariate analyses showed the following significant variables associated with CRP: gender [mean (S.D.) CRP of 16 (19) mg/l in males *vs* 10 (18) mg/l in females; Wilcoxon, $P < 0.0001$], age (Spearman's correlation coefficient, $r = -0.11$; $P = 0.002$), BASFI ($r = 0.13$; $P = 0.0002$), BASDAI ($r = 0.05$; $P = 0.15$) and PGADA ($r = 0.10$; $P = 0.003$). Four variables were retained in the multivariate model (multiple linear regression): the CRP levels were correlated positively with male sex ($P < 0.0001$), BASDAI ($P < 0.0001$) and BASFI ($P < 0.0001$) and negatively with age ($P < 0.0001$).

The multivariate analysis of the logistic regression model associated with an increased CRP >5 mg/l picked up the following variables: age [OR = 0.98; 95% CI 0.97, 0.99; $P = 0.004$], male gender [OR = 2.1; 95% CI 1.5, 2.8; $P < 0.0001$] and BASFI [OR = 1.01; 95% CI 1.004, 1.017; $P = 0.002$]. As an example, an increased CRP was observed in 66, 63 and 55% of patients between 18 and 30, between 30 and 50, and >50 years old, respectively. Similarly, an increased CRP was observed in 58 and 63% of patients with a BASFI (0–100) ⩽40 and >40, respectively.

Fig. 1 Flow chart of the study.

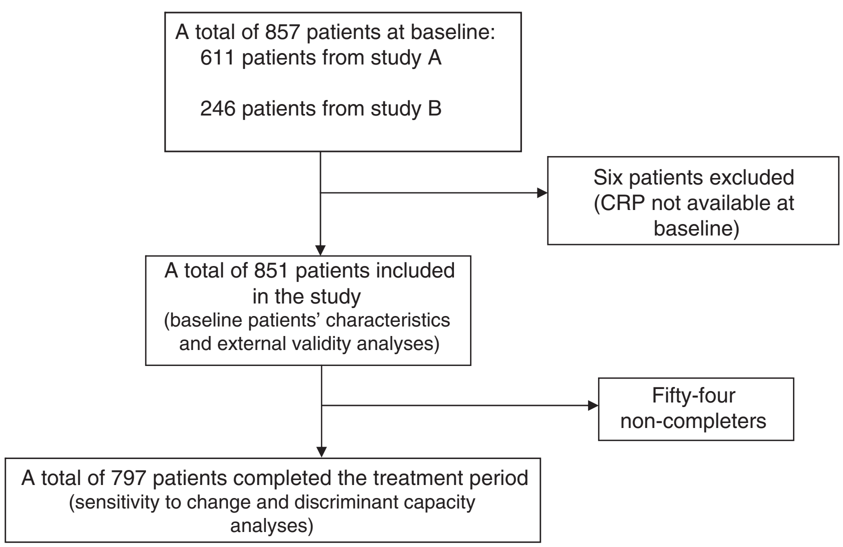


TABLE 1 Baseline characteristics of 851 patients

	Placebo ($n = 231$)	Cox-2 selective inhibitors ($n = 375$)	Non-selective NSAIDs ($n = 245$)	Total ($n = 851$)
Patient characteristics				
Age, mean (S.D.) (median), years	42.5 (11.3) (42.0)	43.2 (11.6) (42.9)	42.9 (12.6) (42.7)	42.9 (11.8) (42.4)
Male, *n* (%)	167 (72.3)	274 (73.1)	176 (71.8)	617 (72.5)
HLA B27 status[a], *n* (%)	58 (76.3)	57 (72.2)	71 (79.8)	186 (76.2)
Disease characteristics				
Disease duration[a], mean (S.D.) (median), years	11.3 (9.1) (9.9)	11.4 (8.6) (7.9)	11.8 (9.7) (9.4)	11.5 (9.2) (9.1)
BASFI, mean (S.D.) (median), 0–100 VAS	50.5 (23.6) (49.9)	49.9 (24.2) (49.4)	47.2 (21.6) (46.4)	49.3 (23.3) (48.5)
BASDAI, mean (S.D.) (median), 0–100 VAS	56.2 (18.8) (56.5)	56.4 (19.3) (57.1)	55.3 (17.8) (56.0)	56.0 (18.7) (56.7)
PGADA, mean (S.D.) (median), 0–100 VAS	68.4 (20.7) (70.0)	65.8 (21.3) (69.0)	63.7 (21.5) (66.0)	65.9 (21.2) (69.0)
Pain, mean (S.D.) (median), 0–100 VAS	72.5 (15.6) (72.0)	70.9 (15.6) (72.0)	69.3 (15.7) (70.0)	70.9 (15.7) (71.0)
CRP, mean (S.D.) (median), mg/l	14.4 (18.3) (7.6)	14.5 (20.5) (7.1)	12.7 (15.7) (7.0)	14.0 (18.6) (7.2)
CRP $>$ 5mg/l, *n* (%)	231 (61.5)	375 (60.5)	245 (62.5)	522 (61.3)

[a]HLA B27 status and disease duration were only available in 244 patients (Study B); VAS: visual analogue scale.

Sensitivity to change and discriminant capacity

The changes after therapy and their calculated SRM are summarized in Table 2. Changes were nil in the placebo group and of higher magnitude in the different subgroups of active drugs.

In the placebo group, the mean (S.D.) change in CRP was 0.9 (15.2) in Study A (12-week duration) and −0.8 (13.5) in Study B (6-week duration), with a mean SRM over placebo of 0.30 and 0.12 in Studies A and B, respectively.

This study clearly demonstrated a significant effect of NSAIDs/coxibs on CRP in AS. No difference was observed between anti-inflammatory drugs (i.e. cox-2-selective *vs* non-selective NSAIDs) or between two doses of the same drug (i.e. celecoxib 200 mg *vs* celecoxib 400 mg).

The comparison of the discriminant capacity (SRM over placebo) of CRP with other conventional variables is summarized in Table 3 by pooling the different active drugs subgroups.

We further evaluated the CRP treatment effect with regard to the baseline CRP. The results presented in Fig. 2 clearly show a 'dose-related' effect: the more the CRP was at the baseline, the higher the SRM was over placebo (Fig. 2).

Discussion

We confirmed the high frequency of increased CRP in patients with painful axial AS (61% in our study) and confirmed the validity of CRP as an outcome measure reflecting the degree of inflammation in AS. This study also suggests that CRP might be correlated with the severity of the disease. Moreover, despite the fact that NSAIDs/coxibs are usually seen as 'pure' symptomatic drugs, this study suggests a relevant treatment effect of NSAIDs/coxibs on CRP in the subgroup of patients with increased CRP at baseline.

The relative frequency of increased CRP in pure axial involvement of AS has not been frequently evaluated. One possible limitation of the present study is that patients were participating in clinical trials. Therefore, the generalization of the observed results might be hazardous. On the other hand, our findings (e.g. mean CRP of 14 mg/l) are similar to those reported by Spoorenberg *et al.* [14] in the study involving outpatients with axial AS not participating in a clinical trial.

An increased CRP was found to be correlated with other markers conventionally considered as reflecting the activity (inflammation) of the disease, such as BASDAI. The higher CRP values observed in males compared with females are more difficult to interpret. Interestingly, this study also found a statistical degree of correlation between CRP and other markers conventionally considered as reflecting the severity (structural change) of the disease, such as BASFI. A limit of the present study is that both concepts (i.e. activity and severity) were only based on patient-reported outcomes. In particular, spinal/sacroiliac MRI findings (suggestive of inflammation) or X-rays/spinal mobility (suggestive of structural deterioration) were not available in this study.

Finally, concerning the evaluation of the validity of CRP, the cross-sectional design of the present study does not permit a definite conclusion. The capacity of an increased CRP at a single point in time to predict a subsequent structural deterioration in the disease requires a long-term longitudinal design or further epidemiological studies.

Our study demonstrates a significant treatment effect of NSAIDs/coxibs on CRP. However, the remaining question is related to the clinical relevance of the observed results. Longitudinal studies evaluating the predictive validity of CRP might provide information on the level of clinically relevant CRP changes. Currently, two other techniques

TABLE 2 Changes in CRP observed in different subgroups of patients and differences when compared with placebo

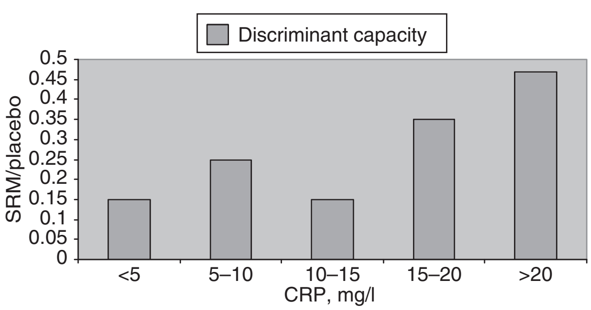
Treatment arm	*n*	Baseline, mean (S.D.)	Changes after therapy, mean (S.D.)	*P*-value[a]	SRM over placebo
Placebo	213	14.1 (18.6)	0.3 (14.7)	0.003	–
Pooled NSAIDs/coxibs	584	13.7 (17.6)	−2.6 (11.7)		0.25
Placebo	213	14.1 (18.6)	0.3 (14.7)	0.01	–
Cox-2-selective inhibitors	355	14.2 (18.6)	−2.7 (9.9)		0.30
Non-selective NSAIDs	229	12.8 (15.9)	−2.5 (14.1)		0.18
Placebo	213	14.1 (18.6)	0.3 (14.7)	0.03	–
Celecoxib 200 mg	199	16.2 (20.4)	−3.2 (10.2)		0.34
Celecoxib 400 mg	156	11.7 (15.7)	−2.0 (9.4)		0.24
Ketoprofen	82	14.3 (16.9)	−1.0 (12.4)		0.10
Naproxen	147	12.0 (15.3)	−3.3 (14.9)		0.25

[a]Comparison with analysis of variance procedure.

TABLE 3 Discriminant capacity of several outcome variables in AS

Variables	Groups	*n*	Baseline, mean (S.D.)	Change, mean (S.D.)	*P*-value	SRM (95% CI)	SRM over placebo
CRP, mg/l	Placebo	213	14.1 (18.6)	0.3 (14.7)	0.003	0.02 (−0.10, 0.17)	0.25
	Pooled NSAIDs/ coxibs	584	13.7 (17.6)	−2.6 (11.7)		−0.22 (−0.33, −0.13)	
BASFI, 0–100 VAS	Placebo	213	50.6 (23.6)	1.7 (22.1)	<0.0001	0.08 (−0.06, 0.21)	0.60
	Pooled NSAIDs/ coxibs	584	49.0 (23.3)	−12.0 (22.8)		−0.53 (−0.61, −0.45)	
BASDAI, 0–100 VAS	Placebo	147	56.1 (19.1)	−2.8 (22.3)	<0.0001	−0.12 (−0.32, 0.11)	0.72
	Pooled NSAIDs/ coxibs	432	55.7 (18.9)	−20.4 (24.2)		−0.84 (−0.88, −0.65)	
PGADA, 0–100 VAS	Placebo	213	68.1 (20.9)	−7.2 (28.8)	<0.0001	−0.25 (−0.39, −0.12)	0.54
	Pooled NSAIDs/ coxibs	584	64.6 (21.4)	−23.6 (30.1)		−0.79 (−0.88, −0.70)	
Pain, 0–100 VAS	Placebo	189	72.7 (15.8)	−15.8 (28.5)	<0.0001	−0.56 (−0.67, −0.39)	0.62
	Pooled NSAIDs/ coxibs	548	70.2 (15.6)	−32.9 (28.0)		−1.18 (−1.29, −1.07)	

FIG. 2 Discriminant capacity of CRP, expressed as SRM over placebo (i.e. SRM of active group minus SRM of placebo group) depending of the level of baseline CRP.



might be used to interpret these results: the first one consists of the comparison of the observed results with the *a priori* defined relevance of a treatment effect (e.g. to consider a treatment effect as nil, mild, moderate and relevant for an observed value of <0.20, 0.20–0.40, 0.40–0.60 and >0.60, respectively). In this view, the observed treatment effect can be considered as mild. Another technique permitting the evaluation of the relevance of the observed results is to compare it with the treatment effect of conventional outcome measures used in AS such as BASDAI, pain and BASFI. In this case, the observed treatment effect of NSAIDs/coxibs on CRP can be considered as one of much lower magnitude.

In conclusion, increased CRP was frequently observed in patients with painful axial AS and was correlated both with activity and functional severity of the disease. The treatment effect of NSAIDs/coxibs was relevant in the subgroup of patients with increased CRP before therapy.

Rheumatology key messages

- Increased CRP is not rare in patients with painful axial AS.
- CRP correlates both with activity and functional severity in axial AS.
- The treatment effect of NSAIDs/coxibs is relevant in patients with pre-treatment increased CRP.

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