pANCA, ASCA, and OmpC Antibodies in Patients with Ankylosing Spondylitis without Inflammatory Bowel Disease

MIRJAM de VRIES, IRENE van der HORST-BRUINSMA, INGRID van HOOGSTRATEN, ADRIAAN van BODEGRAVEN, MARY von BLOMBERG, HANA RATNAWATI, and BEN DIJKMANS

ABSTRACT. ***Objective.*** Patients with ankylosing spondylitis (AS) can suffer concurrently from inflammatory bowel disease (IBD), as ulcerative colitis (UC) or Crohn's disease (CD). Serological markers have been described to diagnose IBD. We investigated IBD serological markers in AS patients without IBD and whether these antibodies enable differentiating patients with AS and IBD from those without IBD.

Methods. Frequencies of perinuclear antineutrophil cytoplasmic antibodies (pANCA), antibodies to the cell-wall mannan of *Saccharomyces cerevisiae* (ASCA), and antibodies to porin protein C of *Escherichia coli* (OmpC) were evaluated in 179 patients: 52 with AS, 50 with UC, 51 with CD, and 26 with IBD and AS. Patient groups were matched for age and sex. All AS patients fulfilled the 1984 modified New York criteria. IBD was ascertained by clinical, endoscopic, and microscopic findings.

Results. In 55% of the AS patients without manifest IBD at least one antibody associated with IBD was observed. pANCA, ASCA (IgA and/or IgG), and OmpC antibodies were found in 21%, 30%, and 19% of the AS patients, respectively. pANCA was more frequently present in AS with concurrent UC than in AS alone (OR 8.2, 95% CI 1.2–55.6), thus being an indicator for UC in AS patients.

Conclusion. Antibodies associated with IBD are detectable in more than half of AS patients without symptoms or signs of IBD. A relatively recent marker in this setting, OmpC antibodies, does not contribute to the differentiation between AS and type of IBD. Presence of pANCA, however, is significantly increased in AS patients who also have UC, and is an indicator to perform endoscopy. These results corroborate a pathophysiological link between AS and IBD. (J Rheumatol First Release September 1 2010; doi:10.3899/jrheum.100269)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS — INFLAMMATORY BOWEL DISEASE
PERINUCLEAR ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES — ASCA
OmpC — TUMOR NECROSIS FACTOR BLOCKERS

Several clinical observations imply a common pathogenetic trunk of ankylosing spondylitis (AS) and inflammatory bowel disease (IBD). About 5%–10% of patients with AS have concurrent IBD, either Crohn's disease (CD) or ulcerative colitis (UC)[1,2,3]. In patients with AS without abdominal complaints, 25%–49% show microscopic lesions in colon biopsies[4,5,6,7,8]. It has been postulated that intestinal inflammation is of (etio)pathogenic importance for development of AS[9]. Chronic IBD is usually diagnosed by means of an ileocolonoscopy including histological sampling, which is an invasive, burdensome, patient unfriendly. and costly procedure. Therefore, use of serological markers associated with bowel disease to select AS patients at risk of IBD could be helpful to increase the likelihood of a positive diagnosis following an invasive procedure. In IBD, several such markers have been proposed to help identify patients at risk for either CD or UC[10,11,12,13]. Previous research in our center showed that in UC perinuclear antineutrophil cytoplasmic antibodies (pANCA) had a sensitivity of 63% and a specificity of 86%[12]. In CD, antiglycan antibodies to the cell-wall mannan of *Saccharomyces cerevisiae* (ASCA) had a sensitivity of 72% and a specificity of 82%[10,12]. Other investigators have reported similar results[10]. An even higher specificity is obtained by combining ASCA and pANCA[12]. Antibodies to porin protein C of *Escherichia coli* (OmpC antibodies) are also observed in CD, present in about 40%

From the Departments of Rheumatology, Clinical Immunology, and Gastroenterology, VU University Medical Centre, Amsterdam, The Netherlands; and Maranatha Christian University, Bandung, Indonesia.

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M.K. de Vries, MD, Department of Rheumatology; I.M.W. van Hoogstraten, MD, Department of Clinical Immunology; A.A. van Bodegraven, MD, Department of Gastroenterology; B.M.E. von Blomberg, MD, Department of Clinical Immunology, VU University Medical Centre; H. Ratnawati, MD, Maranatha Christian University; B.A.C. Dijkmans, MD; I.E. van der Horst-Bruinsma, MD, PhD, Department of Rheumatology, VU University Medical Centre.

Address correspondence to Dr. I.E. van der Horst-Bruinsma, Department of Rheumatology, VU University Medical Centre, Room 3A-64, PO Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: ie.vanderhorst@vumc.nl

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of patients[10,14]. These serological markers, in particular ASCA and OmpC antibodies, are rarely positive (< 5%) in healthy controls[10,14,15,16].

Generally, IBD and AS respond well to treatment with tumor necrosis factor (TNF) blocking agents, although several TNF blockers do not show therapeutic efficacy in IBD. In AS the registered TNF-blocking agents infliximab, adalimumab, and etanercept show effectiveness in up to 70% of patients, but in IBD, etanercept appeared to be ineffective[17]. As most studies are performed in CD, only limited data are available on effectiveness of anti-TNF in UC, but recent studies indicated that infliximab has (limited) efficacy in UC[18]. Identification of AS patients with concurrent IBD could therefore be important in an optimal choice of (costly) biological therapy.

The primary objective of our study was to investigate which serological markers of IBD are elevated in patients with AS who have no symptoms or signs of IBD and whether presence of these antibodies in AS with concurrent IBD enables differentiation from AS without IBD.

MATERIALS AND METHODS

Patients. Consecutive patients with AS and/or IBD were included after matching for age and sex. These patients were invited to participate if their visits and demographic and clinical data were registered and sera were stored for analysis in our biobank.

One hundred eighty-two patients were enrolled in the study: 52 AS patients without symptoms or signs of IBD, 52 patients with UC, 52 patients with CD, and 26 patients with concurrent IBD and AS. Matching was performed to prevent a bias of the serological testing due to age or sex differences between groups. The selected patients regularly visited gastroenterology and rheumatology outpatient departments of the VU University Medical Centre, Amsterdam, The Netherlands, a third-line referral center.

Diagnosis of AS was based on the 1984 modified New York criteria[19]. AS patients with persistent gastrointestinal (GI) complaints or diarrhea, unexplained weight loss, or iron-deficiency anemia were referred to the Department of Gastroenterology to exclude GI disease, and IBD in particular. All AS patients with persistent abdominal complaints underwent endoscopies (n = 10). IBD patients with inflammatory-like back or joint pain were referred to the Department of Rheumatology, where patients were analyzed for presence of sacroiliitis. Patients were consequently moved into the correct patient group and data analysis was performed after final diagnosis, including AS only, AS plus CD, AS plus UC, or CD or UC without AS.

Diagnosis of CD and UC was based on standard endoscopic, histological, and radiographic features[20]. Disease localization and behavior were documented according to the Vienna classification[21].

Outcome measures. Assessment of the serological markers. Most AS patients, and a large number of IBD patients, received anti-TNF-blocking therapy, but all blood samples used for this study were obtained before therapy was started. Examinations were performed in a blinded fashion, without knowledge of patients' clinical information. Sera were frozen at –80°C until testing.

pANCA. Determination of pANCA was performed by an in-house indirect immunofluorescence technique using ethanol-fixed human peripheral blood neutrophils as substrate as described by Linskens, *et al*[12]. Sera were incubated at 1:20 and 1:80 dilutions. Readout was done by visual scoring by 2 readers independently in 3 categories: negative (negative or borderline immune fluorescence at dilution 1:20), weakly positive (positive at 1:20 but negative at 1:80 serum dilutions), or strongly positive (titer ≥ 1:80). To investigate the possibility of a false-positive pANCA due to antinuclear antibodies (ANA) additional testing with HEp-2000® slides (ImmunoConcepts, BMD, Sacramento, CA, USA) was performed in case of a (weakly) positive pANCA test result. Cutoff for positivity was set at 1:80.

ASCA. ASCA-IgA and ASCA-IgG were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (Inova, Uniprom Diagnostics BV, Krimpen aan de IJssel, The Netherlands). The antigen consisted of phosphopeptidomannan (PPM) extracted from *S. cerevisiae*. ASCA ELISA were performed according to manufacturer's instructions; results were expressed as arbitrary units with a cutoff for positivity at 25 U/ml as advised by the manufacturer, resulting in a sensitivity for CD of 49% for ASCA-IgA and 74% for ASCA-IgG, and in 1.4% and 4% positive respectively in healthy controls. Serum was considered positive if either IgA or IgG or both were positive. Serum was considered negative if both ASCA-IgA and ASCA-IgG were negative.

OmpC antibodies. IgA antibodies to bacterial OmpC were detected according to the manufacturer's protocol (Inova, Uniprom Diagnostics BV). The results are presented as arbitrary units with a cutoff for positivity at 25 U/ml.

Serological profiles. The usual UC serological profile was arbitrarily defined as pANCA+ in 1:80, ASCA (IgA or IgG) < 25 U/ml, and OmpC antibodies < 25 U/ml. The classical CD serological profile was arbitrarily defined as pANCA negative or positive in 1:20, ASCA (IgA or IgG) > 25 U/ml, or OmpC antibodies > 25 U/ml.

Statistical analysis. Frequencies and percentages of pANCA, ANA, ASCA-IgA and ASCA-IgG, and OmpC antibodies were calculated in each group of patients. Chi-square analysis or Fisher's test was performed to examine dichotomous variables. Logistic regression analyses were conducted to examine associations between serological markers and serological profiles. The influence of confounders on this relation was investigated. The following variables were investigated: age, sex, and presence of HLA-B27. Statistical analyses were performed with SPSS 15.0 software. The threshold for statistical significance was set at $p < 0.05$.

RESULTS

We recruited 182 patients for the study, 52 patients with AS without IBD, 26 with concurrent AS and IBD (11 AS plus UC, 15 AS plus CD); and 50 patients with UC and 51 with CD, both without AS. Two UC patients and 1 CD patient were excluded as serum samples were unavailable.

Demographic data of these groups were similar (Table 1). Nonsteroidal antiinflammatory drugs (NSAID) were used daily by 67 (86%) of all AS patients, immunosuppressive drugs were used in a minority, and TNF-blocking agents were started in a majority of AS and CD patients (Table 1).

As expected, within the IBD group, pANCA was more frequently seen in UC ($p < 0.0001$), whereas ASCA and OmpC antibodies were more frequent in CD ($p < 0.0001$, $p = 0.006$, respectively; Table 2). These results were comparable with our previous evaluation of pANCA and ASCA in patients with UC and CD[12]. In the overlap group with concurrent AS and IBD, pANCA was more frequent in patients with UC as well ($p = 0.024$); as well, ASCA was more frequently observed in CD although this did not reach statistical significance. OmpC antibodies did not differ between the 2 AS groups.

Prevalences of serological markers in AS without IBD.

Table 1. Patient characteristics (n = 179) and clinical variables.

Characteristic	AS, n = 52	UC, n = 50	CD, n = 51	AS+UC, n = 11	AS+CD, n = 15
Male (%)	29 (56)	23 (46)	21 (41)	5 (46)	6 (40)
Age, yrs, mean (SD)	41 (12)	37 (11)	36 (13)	43 (11)	38 (12)
Caucasian (%)	46 (89)	35 (78)	36 (78)	9 (82)	12 (80)
HLA-B27+ (%)	42 (84)			5 (83)	10 (67)
Peripheral arthritis (%)	21 (40)			1 (9)	1 (7)
Uveitis (%)	16 (31)			1 (9)	0 (0)
CRP at baseline	11 (2.5–163)			9 (2.5–37)	29 (2.5–294)
Duration of IBD, yrs, mean (SD)	NA	8 (7)	11 (9)	9 (8)	15 (12)
BASDAI at baseline, mean (SD)	6.3 (1.6)	NA	NA	6.2 (1.0)	6.0 (1.9)
Vienna classification					
Age: onset < 40 yrs (%)			43 (88)		8 (89)
Behavior					
Inflammatory (%)			17 (35)		6 (67)
Stricturing (%)			13 (27)		3 (33)
Perforating (%)			19 (39)		0 (0)
Localization					
Terminal ileum (%)			10 (20)		0 (0)
Colon (%)			14 (29)		4 (44)
Ileocolonic (%)			24 (49)		5 (56)
Upper GI (%)			1 (2)		0 (0)
Immunosuppressive (%)	3 (6)	5 (10)	4 (8)	3 (27)	4 (27)
Anti-TNF (%)	51 (98)	1 (2)	23 (46)	3 (27)	11 (73)

AS: ankylosing spondylitis; UC: ulcerative colitis; CD: Crohn's disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (0–10); NA: not applicable.

Table 2. Antibodies present in serum of patients (n = 179) with ankylosing spondylitis (AS), ulcerative colitis (UC), Crohn's disease (SD), AS with concurrent UC, and AS with concurrent CD.

Antibody	AS	UC	CD	AS+UC	AS+CD
pANCA IgG (%)	11 (21)	33 (66)	8 (16)	7 (64)	3 (20)
ASCA IgA (%)	10 (19)	4 (8)	19 (37)	1 (9)	4 (27)
ASCA IgG (%)	4 (8)	5 (10)	27 (53)	1 (9)	2 (13)
OmpC antibodies IgA (%)	10 (19)	6 (12)	18 (35)	3 (27)	5 (33)
UC profile (%)	8 (17)	25 (50)	4 (8)	6 (67)	0 (0)
CD profile (%)	13 (28)	3 (6)	27 (54)	2 (20)	4 (27)

pANCA: perinuclear antineutrophil cytoplasmic antibodies, positive: titer ≥ 1:80; ASCA: antiglycan antibodies to the cell wall mannan of *Saccharomyces cerevisiae*, positive: > 25 U/ml; OmpC antibodies: antibodies to porin protein C of *Escherichia coli*, > 25 U/ml.

Presence of any of the 4 serological markers was observed in 55% of AS patients without symptoms or signs of IBD. ASCA (IgA and/or IgG) and OmpC antibodies, markers of CD, were found to be positive in 30% and 19%, respectively, of AS patients without IBD, versus the reported prevalence of 5% or lower in healthy controls[10]. pANCA was found in 21% of the AS patients without IBD.

Differences between patient groups. Differences in frequencies of pANCA between patient groups were not due to ANA: a positive ANA was found in about 25% of each group (results not shown). pANCA was statistically significantly more frequent in AS with concurrent UC than in AS alone (OR 8.2, 95% CI 1.2–55.6, adjusted for the presence of HLA-B27), thus being an indicator for UC in AS. Moreover, the serological profile for UC differentiated between AS patients with concurrent UC versus AS alone. In patients with CD no serological marker or profile differentiated between AS with concurrent CD and AS alone. No association was found between presence of HLA-B27 and presence of any of the serological markers, or presence of IBD in AS patients (data not shown).

Colonoscopy. All AS patients without IBD who had persistent abdominal complaints underwent endoscopies and IBD was excluded. One out of 10 patients had signs of microscopic chronic inflammation in the cecum, but there was not enough evidence in support of IBD, according to the usual definition[20]. The 10 patients did not have more frequent peripheral arthritis, higher C-reactive protein, or positive

serology (pANCA, ASCA-IgA or ASCA-IgG, anti-OmpC), nor did they have higher titers of anti-OmpC compared to the AS patients without GI complaints. Hence, this particular cohort/group could not be distinguished by serological profile (data not shown).

DISCUSSION

Our study reports on the prevalence of serological markers associated with IBD (pANCA, ASCA, and OmpC antibodies) in patients with AS. For proper evaluation, 3 groups of patients with chronic inflammatory diseases were included: patients with AS, with IBD, and with concurrent AS and IBD.

All the serological markers measured were frequently observed in AS patients: pANCA, ASCA-IgA, and ASCA-IgG antibodies in 21%, 19%, and 8% of the 52 AS patients, respectively. Further, we demonstrated for the first time that OmpC antibodies are highly prevalent in AS patients (19%). These markers, notably ASCA and OmpC antibodies, rarely occur in healthy controls[10]. The frequencies of serological markers in AS patients with concurrent UC or CD, except for OmpC antibodies, were comparable with our reference findings in UC or CD alone. Our findings are in concordance with reports showing increased prevalence of pANCA[22], in particular ASCA, in patients with AS[15,22,23]. Positive ASCA-IgA was found in 19% of AS patients without IBD and in 27% in the 15 patients with AS and CD, which is not in concordance with the study of Hoffman, *et al*[23], who found no difference among positive ASCA tests in a small series of AS patients with IBD (n = 6) and without IBD (n = 12). The observed prevalence for the various markers in these series, however, was higher than that reported in a recent study by Mundwiler, *et al*[24].

pANCA was statistically significantly more frequently present in AS patients with concurrent UC than in AS alone, with an OR of 8.2 (95% CI 1.2–55.6). pANCA thus might be a valuable tool to screen AS patients with abdominal complaints: if pANCA is present, performance of an endoscopy is indicated.

Despite this high prevalence of IBD markers in AS patients, our study might be flawed due to the fact that invasive colonoscopy was performed in 10 of 52 AS patients (20%). Indeed, colonoscopy was performed only in patients with persistent GI complaints, because the *a priori* chance of detecting IBD in asymptomatic patients is considered to be very low. However, even in AS patients with intestinal symptoms, and therefore a relatively "high-risk" group, the frequency and level of antibodies did not differ from the asymptomatic patients. The explanation for the increased levels of IBD markers in AS is in accord with the studies performed by Mielants, *et al*[25], who found a high number of mucosal lesions in asymptomatic AS patients, in particular in the terminal ileum, without convincing macroscopic signs of inflammation by microscopic examination. Intestinal damage (and increased intestinal leakage) itself may be associated with increased IBD markers, but our study was not designed to confirm this association. Interpretation is thwarted due to group sizes. It is interesting, however, that 6.5% of cases reported by Mielants developed IBD after 2–9 years of followup[8].

Involvement of the GI tract in AS can be interpreted in 3 ways: as an aberrant immune response following a GI infection, as part of an inflammatory disease sharing a common genetic background, or as a result of intestinal leakage due to treatment with NSAID.

As a first hypothesis, AS is induced by a pathogenic microbial, such as Klebsiella[26,27], similarly to the onset of another form of spondyloarthropathy, i.e., reactive arthritis, which is related to the culprit intestinal pathogen (Salmonella species), which induces an aberrant immune response. However, previously no correlation was found between the presence of ASCA in serum and Saccharomyces in the intestine[28]. A second hypothesis assumes that a common genetic background in combination with external factors triggers an (auto) immune response against different organs, such as intestines, spine, joints, eyes, or skin[1,29]. Corroborating this hypothesis, extraspinal manifestations are frequently observed in AS patients, such as those with uveitis, which also occurs in IBD.

The third hypothesis is that serological IBD markers, notably ASCA and OmpC antibodies, reflect intestinal damage. Fitting in with this hypothesis is that in celiac disease, which is associated with damage to the intestinal barrier, the prevalence of ASCA is increased[30]. Moreover, chronic use of (maximum dosages of) NSAID may result in increased intestinal leakage, leading to an (auto) immune response against intestinal antigens[31]. From this perspective one might expect higher prevalence of ASCA in other patient groups taking NSAID on a regular basis, such as patients with rheumatoid arthritis, but these data have not been reported.

Together, IBD-associated serological markers are insufficiently sensitive for identifying IBD in AS, but presence of pANCA might differentiate AS patients with concurrent UC from patients without UC, and these patients are candidates for colonoscopy.

We demonstrate that presence of IBD-associated markers in AS patients is indicative that AS and IBD share a similar pathophysiological origin. These findings apply to AS patients with and without proven IBD since serum markers were also found in AS patients without (symptoms of) IBD.

Prospective followup of patients with AS and positive IBD serology markers in comparison with seronegative patients might shed new light on this discussion and contribute to the decision on whether to perform ileocolonoscopy, and on which TNF-blocking agents might be most effective, as some (e.g., etanercept) are not effective in colitis[16].

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Corrections

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