Published in: American Journal of Gastroenterology (2002), vol. 97, pp. 1458-1462.
Status: Postprint (Author's version)

Serological Markers for Prediction of Response to Anti-Tumor Necrosis Factor Treatment in Crohn's Disease

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Objectives: The use of monoclonal anti-tumor necrosis factor (TNF) antibodies (infliximab, Remicade) is a new therapeutic approach for severe refractory luminal or fistulizing, Crohn's disease (CD). However, up to 30% of patients do not respond to this treatment. So far, no parameters predictive of response to anti-TNF have been identified. Our aim was to determine whether serological markers ASCA (anti-*Saccharomyces cerevisiae* antibodies) or pANCA (perinuclear antineutrophil cytoplasmic antibodies) could identify Crohn's patients likely to benefit from anti-TNF therapy.

Methods: Serum samples of 279 CD patients were analyzed for ASCA and pANCA before anti-TNF therapy. A blinded physician determined clinical response at week 4 (refractory luminal CD) or week 10 (fistulizing CD) after the first infusion of infliximab (5 mg/kg).

Results: Overall, there was no relationship between ASCA or pANCA and response to therapy. However, lower response rates were observed for patients with refractory intestinal disease carrying the pANCA+/ASCA- combination, although this lacked significance ($p = 0.067$).

Conclusions: In this cohort of infliximab-treated patients, neither ASCA nor pANCA could predict response to treatment. However, the combination pANCA+/ASCA- might warrant further investigation for its value in predicting non-response in patients with refractory luminal disease.

INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic intestinal disorders characterized by frequent flare-ups alternating with periods of remission. For many patients with active disease, corticosteroids, despite their side effects, are still the preferred first line therapy, although this treatment is not disease modifying. Recently, monoclonal chimeric antibodies (infliximab) to tumor necrosis factor (TNF), a drug with a more specific mechanism of action, have proved to be effective in both refractory and fistulizing CD. Approximately 70% of patients show response, with up to one third of patients entering clinical remission by 4 wk after a single-dose infusion (1). For fistulizing disease, 68% of patients showed a response and 55% had complete stop of drainage in the study by Present *et al.* (2). Infliximab is also the first drug that may induce important or complete mucosal healing in the short term (3, 4).

However, for unknown reasons, the treatment fails in up to 30% of patients. Because of the severe problem of treatment refractoriness, factors that could predict response would be very helpful for designing treatment strategies in refractory IBD. So far, no reliable marker with sufficient predictive value for assessing treatment refractoriness could be identified.

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Anti-*Saccharomyces cerevisiae* (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA) are serological markers associated with CD and UC, respectively. ASCA are antibodies directed against oligomannosidic epitopes on the cell wall of *S. cerevisiae.* Approximately 60% of CD patients carry these antibodies (5-9). In addition, pANCA has been correlated with UC with a sensitivity of 60-80% (10-13). Of the CD patients, 5-10% also express pANCA. Mostly these patients present with left-sided colitis and respond well to topical therapy (14), although this has not been universally found (15). It was suggested that pANCA have predictive value with regard to the development of pouchitis after ileoanal pouch anastomosis for UC (16-18). Their presence in UC has also been associated with aggressive disease and early surgery (19).

Because of their high specificity, ASCA and pANCA might be useful for differentiation between various phenotypes of IBD, but their low sensitivity makes the diagnostic value of these markers questionable. However, it has already been suggested that these antibodies might determine response to new therapeutic agents (20). Therefore, the aim of this study was to determine whether ASCA, pANCA, or a combination of both markers could define patient subgroups likely to benefit from anti-TNF treatment.

MATERIALS AND METHODS

Study Population

A total of 279 patients with active Crohn's disease who were included in an expanded access program for treatment with infliximab (Schering-Plough NV, study P 01246-1) were studied. Of these, 89 patients received infusions for fistulizing Crohn's disease and 190 for refractory luminal CD. Demographic characteristics and baseline clinical information are given in Table 1. The diagnosis of Crohn's disease was based on internationally accepted criteria (21).

The Crohn's Disease Activity Index (CDAI) (22) was calculated before infusion and at week 4 (refractory CD) or week 10 (fistulizing CD) after first infusion. Moreover, a physician blinded to the serological markers scored clinical response at week 4 or week 10. For refractory CD, a single infusion was given at week 0, according to the study protocol; response was considered complete if CDAI dropped to <150 or partial if CDAI decreased by >70 points (1). Patients with fisrulizing CD, who were treated with three consecutive infusions at week 0, 2, and 6, were considered complete responders in case of complete stop of drainage from the fistulas and as partial responders when a decrease in 50% of the number of draining fistulas at two consecutive visits was seen (2). Both complete responders and partial responders were taken as responders.

Whole venous blood was obtained at the first screening visit before inclusion in the trial and at week 4 (refractory disease) or week 10 (fistulizing disease) after first infusion. Serum was separated after clotting by centrifugation and subsequently stored at -80°C until performance of the ASCA and pANCA assays. Serum C-reactive protein (CRP) was measured before treatment at week 0 and at week 4 or week 10, respectively, after anti-TNF infusion.

All patients gave informed consent and the Ethical Board of our institution approved the study.

Table 1. *Demographic and Baseline Clinical Characteristics of the Study Population*

Characteristic	Total (n = 279)	Fistulizing (n = 89)	Refractory (n = 190)	Significance (*p*)
Female/male	177/102	61/28	116/74	ns
Mean age [range] (yr)	36.2 [15-74]	38.2 [16-71]	35.3 [15-74]	0.041
Mean age of initial diagnosis [range] (yr)	25.6 [7-71]	25.8 [8-61]	25.5 [7-71]	ns
Mean CDAI before treatment [range]	257 [11-609]	204 [17-480]	276 [11-609]	<0.001
Mean CRP before treatment [range] (mg/L)	27.8 [<3-163.4]	23.6 [<3-107.4]	29.3 [<3-163.4]	ns
Concomitant treatment				
Steroids	113	29	84	
5-ASA	122	44	78	ns
Immunosuppressives (azathioprine, 6MP, MTX)	151	52	99	

6MP = 6-mercaptopurine; MTX = methotrexate.

ASCA ELISA

The ASCA was measured by a standardized ELISA using microtiterplates coated with phosphopeptidomannan (PPM), obtained through the Laboratoire de Parasitologie, Mycologie of the Center Hospitalier Universitaire (CHU) Lille, France (D. Poulain). A quantity of 100 μl of serum, diluted at 1/1000 in TNT, was added to each well, together with one positive and one negative control. Alkaline phosphatase-labeled goat antihuman IgG, IgA, IgM (heavy and fight chains) diluted at 1/1000 (100 μl) was used (Zymed Laboratories, San Fransisco, CA) as conjugate and substrate MAGIA (Merck Belgolabo, Overijse, Belgium) for alkaline phosphatase was added to obtain a color reaction. Plates were read at 405 nm on an automatic photometer (ANTHOS ht II). Absorbance of the individual sera was expressed relative to the absorbance of a pool of sera collected from well characterized CD patients. All determinations were done in double and the mean absorbance of both determinations was calculated. Previously, we showed that there is excellent reproducibility of measurements with this assay (r = 0.993) (23). Based on receiver operating characteristic (ROC) curves, samples displaying an absorbance ≥3.12% were considered positive.

pANCA Indirect Immunqfluorescence

The pANCA was determined in the Laboratory of Immunology of the UZ Gasthuisberg (Leuven, Belgium) by indirect immunofluorescence (IIF) using ethanol-fixated neutrophil slides (Inova Diagnostics, San Diego, CA). Sera were incubated at a 1/40 dilution for 30 min at room temperature, washed and incubated with fluorescein isothiocyanate-labeled rabbit antihuman IgG immunoglobulin (Inova Diagnostics). Slides were then examined under UV using a Leitz Wetzler Orthoplan microscope (Germany). Sera that exhibited fluorescence on IIF were titred to endpoint. Interference by antinuclear antibodies, which may mimic the pANCA pattern, was ruled out by using formalin-fixed cells (Inova Diagnostic) as described by Wiik (1989) (24). Cut-off value for positivity was set at 1/40.

Statistical Analysis

Comparison of different groups was done using the χ^2 test or Fisher's exact test when appropriate. The paired *t* test was used to analyze paired data on CDAI and CRP. The threshold for statistical significance was set at α = 0.05.

RESULTS

From the total group of 279 Crohn's patients studied, 211 patients (76.0%) were responders (with 53.3% entering clinical remission), 59 (21.0%) were nonresponders, and nine (3.0%) patients could not be evaluated because of confounding factors (psychiatric disorders, n = 3; short bowel syndrome, n = 1; pouchitis, n = 1; stoma, n = 1; acute surgery, n = 2; liver transplant, n = 1). These nine patients were not included in further analysis. The response and nonresponse rates did not differ among fistulizing (75.0%, 25.0%) or refractory luminal subgroups (79.0%, 21.0%).

Of 270 CD patients analyzed, 23 (9.0%) were pANCA positive and 129 (48.0%) had ASCA antibodies.

Neither ASCA nor pANCA alone had any significant predictive value toward anti-TNF treatment response either in the total group nor in one of the subgroups (fistulizing or refractory luminal disease) (Table 2).

Further the combination of both markers was studied, but again no significant relation between response to treatment and any marker combination was seen (Table 2). However, in the patient subgroup with refractory luminal CD a trend toward nonresponse for patients carrying the combination ASCA-/pANCA+ was seen (Fig. 1), although this strictly lacked significance (χ^2 = 7.2; p = 0.067; df = 3). Of the 10 patients with this combination, five were nonresponders and three patients had only partial response. Nine of these patients presented with pure left-sided colitis. In contrast, all four ASCA-/pANCA+ patients in the fistulizing group were responders. Three had a complete response. These three patients had involvement of the ileum as well as the colon. The one patient with partial response had pure left-sided colitis.

Table 3 represents the calculated sensitivity, specificity, and predictive values for the serological markers and their combinations. Regarding the findings above, we were especially interested in the ASCA-/pANCA+ combination. In the subgroup of refractory disease the positive predictive value toward response is 50%, whereas in the fistulizing group it is 100%.

Finally, the correlation between the clinical response score, based on CDAI, and serum CRP levels was examined. For the total patient group, CRP levels at baseline were not different among the responders and nonresponders ($p = 0.72$), neither were the CDAI levels ($p = 0.23$). After anti-TNF treatment, a significant drop in CRP was observed only in the responder group. This was seen for the total group as well as for the refractory and fistulizing subgroups separately (Table 4).

Table 2. *Frequency of Serological Markers ASCA and pANCA (total n = 270)*

	Total (n = 270)		Refractory CD (n = 183)		Fistulizing CD (n = 87)	
Markers	Response	Nonresponse	Response	Nonresponse	Response	Nonresponse
ASCA+	101/129 (86.1%)	28/129 (13.9%)	67/81 (82.7%)	14/81 (17.3%)	34/48 (70.8%)	14/48 (29.2%)
ASCA-	111/141 (78.0%)	31/141 (21.9%)	79/102 (77.5%)	23/102 (22.5%)	31/39 (79.5%)	8/39 (20.5%)
pANCA+	17/23 (73.9%)	6/23 (26.1%)	11/16 (68.7%)	5/16 (31.3%)	6/7 (85.7%)	1/7 (14.3%)
pANCA-	194/247 (78.5%)	53/247 (21.5%)	135/167 (80.8%)	32/167 (19.2%)	59/80 (74.7%)	21/80 (25.3%)
ASCA+/pANCA+	8/9 (88.9%)	1/9 (11.1%)	6/6 (100.0%)	0/6 (0.0%)	2/3 (66.7%)	1/3 (33.3%)
ASCA+/pANCA-	93/120 (77.5%)	27/120 (22.5%)	61/75 (81.3%)	14/75 (18.7%)	32/46 (69.6%)	14/46 (30.4%)
ASCA-/pANCA+	9/14 (64.3%)	5/14 (35.7%)	5/10 (50.0%)	5/10 (50.0%)	4/4 (100%)	0/4 (0.0%)
ASCA-/pANCA-	101/127 (79.5%)	26/127 (20.5%)	74/92 (80.4%)	18/92 (19.6%)	27/35 (77.1%)	8/35 (22.9%)

Table 3. *Sensitivity, Specificity, PPV, and NPV for the Serological Markers and Their Combination in (a) the Total Group, (b) the Subgroups of Refractory CD, and (c) the Subgroup of Fistulizing Disease*

	Response				Nonresponse			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Total group								
ASCA	0.48	0.53	0.78	0.22	0.47	0.52	0.22	0.78
pANCA	0.08	0.90	0.74	0.21	0.10	0.92	0.26	0.79
ASCA+/pANCA+	0.04	0.98	0.89	0.22	0.02	0.04	0.11	0.78
ASCA+/pANCA-	0.44	0.54	0.78	0.21	0.46	0.56	0.23	0.79
ASCA-/pANCA+	0.04	0.92	0.64	0.21	0.08	0.96	0.36	0.79
ASCA-/pANCA-	0.48	0.56	0.80	0.23	0.44	0.52	0.20	0.77
Refractory CD								
ASCA	0.46	0.62	0.83	0.23	0.38	0.54	0.17	0.77
pANCA	0.08	0.86	0.69	0.19	0.14	0.92	0.31	0.81
ASCA+/pANCA+	0.04	1.00	1.00	0.21	0.00	0.96	0.00	0.79
ASCA+/pANCA-	0.42	0.62	0.81	0.21	0.38	0.58	0.19	0.79
ASCA-/pANCA+	0.03	0.86	0.50	0.18	0.14	0.97	0.50	0.82
ASCA-/pANCA-	0.51	0.51	0.80	0.21	0.49	0.49	0.20	0.79
Fistulizing CD								
ASCA	0.52	0.36	0.71	0.21	0.64	0.48	0.29	0.79
PANCA	0.09	0.95	0.86	0.26	0.45	0.91	0.14	0.74
ASCA+/pANCA+	0.03	0.96	0.67	0.26	0.04	0.97	0.33	0.74
ASCA+/pANCA-	0.49	0.39	0.70	0.21	0.61	0.51	0.30	0.79
ASCA-/pANCA+	0.06	1.00	1.00	0.27	0.00	0.94	0.00	0.73
ASCA-/pANCA-	0.42	0.65	0.77	0.28	0.35	0.58	0.23	0.72

Figure 1. *Percentage of responders/nonresponders in function of marker combinations ASCA/pANCA for patients with refractory CD (n = 183).*

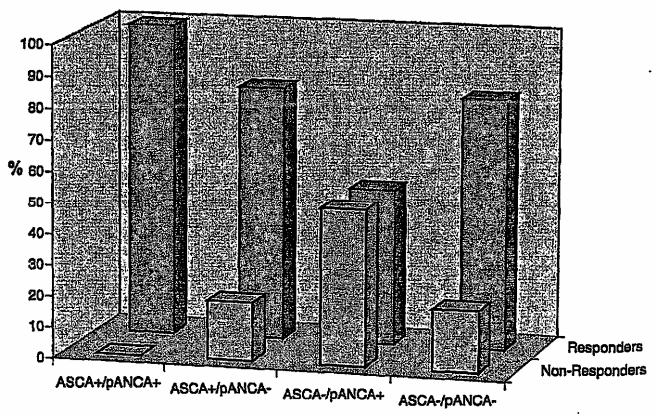

Table 4. *CDAI and CRP According to Response in the Refractory and Fistulizing Subgroups*

	Total		Refractory		Fistulizing	
	Response	Nonresponse	Response	Nonresponse	Response	Nonresponse
CDAI						
Mean baseline CDAI	258	312	272	321	218	282
Mean CDAI difference	-139	-32	-149	-16	-109	-73
Significance	$p < 0.001$	ns	$p < 0.001$	ns	$p < 0.001$	ns
CRP (mg/L)						
Mean baseline CRP	28.94	26.34	29.80	28.57	26.36	20.20
Mean CRP difference	-19.28	-4.49	-20.14	-4.59	-16.67	-6.45
Significance	$p < 0.001$	ns	$p < 0.001$	ns	$p < 0.001$	ns

DISCUSSION

Monoclonal antibodies to anti-TNF are a breakthrough for the treatment of refractory Crohn's disease. The drug also has impressive potential of fistula healing. The fact that one third of patients show no response makes the search for predictive factors for response very important. Again this shows that the pathogenesis of IBD is complex and only little understood. Assessing risk factors or predictors of therapeutic outcome has great potential in medicine; patients likely to benefit from certain drugs can be selected in this way, with greater success rates and lower costs as direct consequences.

In this study, the value of serological markers ASCA and pANCA in predicting response to anti-TNF treatment was assessed. Of all patients evaluable for response, 78.1% responded to the treatment (remission or partial response) and 21.9% had no response. These figures are in line with previous reports (1, 2). The prevalence of ASCA (48.0%) and pANCA (9.0%) are also consistent with other series in the literature (6, 7, 9).

Neither ASCA nor pANCA, either alone or in combination, could predict response to anti-TNF treatment. For the marker combination ASCA-/pANCA+ higher nonresponse rates were observed in the subgroup of patients with refractory luminal disease, although this did not reach significance. Interestingly, in this respect is that also other investigators very recently associated distinct ANCA patterns with differences in response to infliximab, including pANCA positivity and poor response (25, 26).

The fact that the ASCA-/pANCA+ subgroup lacked significance in our study might be due to the small number of patients presenting with this specific combination of markers (14/270; 5.2%). Because the specific marker combination ASCA-/pANCA+ is expected to be rare among CD patients, studying even larger cohorts of patients will be necessary to prove its true value in predicting response. Furthermore, and remarkably, the trend was seen only in the refractory subgroup and in patients with fistulizing disease, and this marker combination responded well to infliximab. This raises the question as to whether these two behavioral types of Crohn's disease could be different entities.

The evolution in CRP correlated well with the clinical response score, based on CDAI. For responders, a significant drop in CRP was seen, whereas this drop lacked for nonresponders. Because the CDAI is partially based on subjective data (as patients have to score their general well-being and rate their pain), response could therefore more objectively be scored using CRP. We observed significantly lower baseline CDAI levels in fistulizing CD compared with refractory CD (Table 4), probably a consequence of different symptoms and medication, parameters implicated in the CDAI. This difference in baseline levels was not observed for the CRP. Therefore, CRP levels could give a more standardized vision of the disease activity status.

In conclusion, this study examined the role of serological markers in predicting therapy response to infliximab. Neither ASCA, pANCA, nor their combination could predict response. However, the question remains whether the marker combination pANCA+/ASCA- is predictive of nonresponse to infliximab in CD patients with severe refractory luminal disease. Finally, clinical response, which is now assessed based on CDAI differences, can be scored more objectively by means of CRP levels, as this parameter correlates well with therapy outcome.

Acknowledgment

This study was made possible with a grant from Schering Plough Belgium.

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