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Research Article

Biomarkers in Enteropathic Arthritis

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Abstract

Inflammatory Bowel Disease (IBD)-associated arthritis is called Enteropathic Arthritis (EA) which is classified among the group of Spondyloarthritis (SpA), because its presentation is variable. The current trend is to classify them as autoinflammatory rather than autoimmune diseases, since no antibodies have yet been identified. The study of biomarkers (BM) will help us with early identification and hence, to provide treatment in the early stages, prior to radiographic progression, which will enable prompt identification of the disease phenotype. 42 patients diagnosed with IBD were included, of which 48% were females; the mean age of the study group was 48.12 ± 5.02 (95% CI). The average time of evolution of disease was 37.57 ± 14.28 months; most patients referred to the rheumatologist had a diagnosis of ulcerative colitis (83%). According to our analysis, we were able to determine that the three most significant variables influencing the development of sacroiliitis were: Lactoferrin, ANCA and HLA B27 ($p < 0.5$). The variable that can be ruled out because of its almost neglectable contribution was fecal calprotectin.

More Information

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Introduction

The tests that link serological biomarkers (BM) to the behavior and phenotype of inflammatory bowel disease (IBD) have grown significantly over the last few years; however, there are notable differences among the various populations, particularly when dealing with miscegenation, which is the standard in Latin America [1,2].

Until now, the anti-*Saccharomyces cerevisiae* antibodies (ASCA) and the perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are the best BM studied in IBD [3,4]. The diagnostic certainty of the independent study of these BM has been outmatched by the combination of its results, resulting in improved differentiation between Crohn's Disease (CD) and ulcerative colitis (UC) [5,6]. The ASCA+/p-ANCA– phenotype is characteristic of CD, whilst the ASCA–/p-ANCA+ phenotype is characteristic of UC [5-8]. The atypical pattern of the p-ANCA (x-ANCA) has been recently recognized with growing interest, considering it may be a useful tool to be able to differentiate the various forms of IBD [9]. However, the association of BM in Enteropathic Arthropathies (EA) is uncertain, since the various study and control groups for these types of diseases (ACR/EULAR/Spartan/ASAS/ESSG) have only agreed on classifying them as another type of Spondyloarthritis (SpA); some include celiac disease and arthritis associated with bariatric surgery, and others rule out Whipple disease and collagenous colitis [5,10].

To further complicate matters in EA, there are three forms of presentation: peripheral enteroarthritis (Type 1), axial enteroarthritis (Type 2), and a so called "without arthritis" (Type 3) [11]. The latter presents with arthralgias, enthesitis, peritendinitis, and hypertrophic osteoarthropathy [5,12,13]. Type 1 is divided into pauciarticular and polyarticular. Type 2 in inflammatory bowel disease behaves as idiopathic ankylosing spondylitis or as an asymptomatic sacroiliitis [14]. Though, different from what usually happens in peripheral arthritis, the axial presentation evolves independently from IBD and the clinical manifestations are unrelated with the remission periods and exacerbation, or with the localization or extension of the intestinal disease [15,16]. Moreover, the onset of axial symptoms is frequently independent and tends to precede the gut disease by several years [17,18].

The prevalence of IBD in patients with SpA has been estimated at around 5 to 10%, but almost 50% of the patients

with SpA present with subclinical inflammation. From the viewpoint of IBD, 3% of patients experience concomitant EA and 13% have peripheral SpA, but the radiographic sacroiliitis – whether symptomatic or subclinical – may compromise half of the patients with IBD [5,20,21].

Patients and methods

42 patients referred from the Gastroenterology department, with a diagnosis of ulcerative colitis (UC) and Crohn's disease (CD) were included; these patients had no previous history of SpA and were subject to the criteria for EA according to the ESSG (European Spondyloarthropathy Study Group), in addition to undergoing plain X-rays and MRI, pursuant to the ASAS/OMERACT (*Outcome Measures in Rheumatology Network)* protocol, under the responsibility of the radiology service of our hospital, by two expert radiologists. Blood samples were drawn for routine laboratory testing, including CBC, blood chemistry panel, in addition to acute phase reactants (ESR/CRP), as well as a blood sample for biomarkers: ANA, HLA B27, ASCA IgG, ASCA IgA and ANCA and a fecal sample to measure lactoferrin and fecal calprotectin.

Both groups of patients were assessed in terms of their clinical characteristics, family history of autoimmunity, extraintestinal characteristics including skin, ocular, cardiovascular, and pulmonary. The study was approved by the HUC/UCV Bioethics Committee prior to drawing the blood samples and completing the patient's form and a copy of the informed consent was delivered and explained to the patient. The ANA, ANCA and ESR tests were conducted in our rheumatology laboratory on the first floor of our clinic; the HLAB27, ASCA IgA, ASCA IgG tests were conducted at the UCV immunology institute. Fecal calprotectin and lactoferrin tests were conducted by a private laboratory (InmunoXXI) and were paid from the study fund of our study group (GRUVES) and in some cases by Abbvie® Laboratories.

The patients diagnosed with EA were then classified based on their severity, based on the collection of clinical and laboratory data, imaging studies as well as a history of joint replacement prosthesis, and if the patient had undergone any arthrodesis, laparotomies and/or hemicolectomy procedures. Activity and severity information was collected via DAS28, BASDAI and BASFI, as well as information about the type of treatment received: DC- ART, glucocorticoids, Anti-TNF therapy, NSAIDs.

Statistical analysis

The data obtained from the research were uploaded and processed using the IBM SPSS 23.0 software in order to:

a) Obtain the basic statistics of the most relevant variables

b) Determine the relationship among the various variables by obtaining the matrix containing Spearman's correlation coefficients

c) Do a logistic regression analysis to identify the most relevant variables in predicting the presence of the disease.

Results

a) Descriptive Statistics

A total of 42 patients diagnosed with IBD were included, with 48% females and a 95% confidence interval for the mean age of the study group of 48.12 ± 5.02, while the 95% CI for the mean time of disease evolution was 37.57 ± 14.28. Most of the patients referred to rheumatology had a diagnosis of UC (35 patients), 90% were receiving Anti-TNF-α treatment, over 60% received glucocorticoids, and half of them received sulfasalazine. Only 8 patients presented with HLA B27 (+) and the fecal calprotectin was negative in all patients (Table 1).

ANA was positive in 17 patients (40%), 53% of the patients were Type 2, 19% (8 patients) Type 3 and the rest were EA type 1 (28%). Both ANCA and ASCA IgG were present in only 5 patients in the trial. BASDAI was only administered to the 8 type 2 patients, resulting in a value of 3.54 ± 2.3, while only 5 of them had a BASDAI ≥ 4.0. DAS 28 6.34 ± 1.12. The majority of the patients with Type 2 EA presented with HLA B27 (75%; $p < 0.005$). Two patients who after gastric bypass surgery developed oligoarticular pathology with inflammatory axial pain and the presence of HLA B27 were included (Table 2).

All patients underwent imaging studies to screen for sacroiliitis; conventional X-rays with oblique and Fergunson projections were ordered, in addition MRI according to the ASAS/OMERACT protocol (Table 3), identifying 74% with active sacroiliitis and bone edema following STIR. Under conventional radiology, 23% presented with bilateral but asymmetric grade III sacroiliitis, 37% Grade II sacroiliitis, and 17% presented with anchyloses (Grade IV).

b) Spearman's correlation

Spearman's correlations for: ESR, CRP, ANA, ASCA, Lactoferrin, Calprotectin, and the significance of the test: Ho: correlation coefficient = 0 , vs. H1: correlation coefficient ≠0 are shown in table 4.

c) Logistic Regression

The logistic regression taking Y as a variable: the presence of sacroiliitis and as explanatory variables: ANA, ANCA, ASCA, HLA B27, Calprotectin. Lactoferrin gave in the Hosmer Lemeshow test a p - value of 0.779, implying that the good model adjustment hypothesis is not ruled out (Table 5).

Radiographic progression model considering the following variables: HLA B27/lactoferrin was 52.4 5%, for the variables lactoferrin/ANCA 52.4%, but the triplet: Lactoferrin/ANCA/HLA B27 was 66.7% ($p < 0.5$). However, the Calprotectin variable value was 1.1% ($p > 0.9$).

Table 1: Characteristics and distribution of patients referred to rheumatology.

Gen	Female:20 (48%) Male:22 (52%)
Age, year	48.12 ± 5.02
Diagnoses	URC35 (83% CD5 (12%) Other2 (5%)
Esr	43.86 ± 9.36
Crp	24.56 ± 6.86
Evolution of the disease (months)	37.57 ± 14.38
Treatment	Glucocorticoids 29 (69%)
	Sulfasalazine 21 (50%)
	Azathioprine 11 (26%)
	Methotrexate 12 (29%)
	Anti TNF 38 (90%)
	Others 4 (10%)
Sacroiliitis	31 (74%)
Ana	17 (40%)
Anca	5 (12%)
Asca iga	13 (31%)
Asca igg	5 (12%)
Lactoferrin	6 (14%)
Calprotectin	92.7 ± 28.3
Hla b27	8 (19%)

*URC: Ulcerative Rectocolitis; CD: Crohn's Disease; ESR: Erythrocyte Sedimentation Rate; By Westergren (Positive > 20 mm In Females And > 15 In Males); CRP: C-Reactive Protein (Positive > 6 Mg/Dl); Anti-Tnf A Anti-Tumor Necrosis Factor Alpha Biologics; Other Drugs Such as Non-Steroid Anti Inflammatory Drugs/Cyclosporin; Ana Antinuclear Antibodies Measured With Hep-2; Anca Anti-Neutrophil Cytoplasmic Antibodies (Measured Through Indirect Immunofluorescence); Asca Anti-Saccharomyces Cerevisiae Antibodies (Measured With Elisa); Fecal Lactoferrin Measured Through Latex Agglutination; Fecal Calprotectin Measured With Elisa; Hla B27 Histocompatibility B27 Antigen (Measured With Flow Cytometry).

Table 2: EA type distribution according to gender and biomarker.

	Type 1	Type 2	Type 3	$p < 0.05$
Gender F/M (%)	34/31	9/67	45/2	
ANA	4	5	8	0.789
ASCA IgA	4	4	5	0.345
ASCA IgG	2	1	2	0.125
ANCA p	1	3	-	0.283
ANCA c	-	1	-	0.987
HLA B27	-	7	1	0.001*
Lactoferrin	1	2	3	
Calprotectin	-	-	-	-

Table 3: Distribution of patients with Sacroiliitis.

		Sacroiliitis		
		Positive	Negative	Total
Diagnosis	URC	16 (38.1%)	19 (45.24%)	35
	EC	4 (9.52%)	1 (2.38%)	5
	Other	1 (2.38%)	1 (2.38%)	2
	Total	21	21	42*

*The percentages refer to the total of 42 patients observed.

The elevation of acute phase reactants (ESR/CRP) as a positive predictor of the progression of sacroiliitis in type 1 and type 3 EA resulted in an OR of 3.65 and 5.08. Respectively ($p < 0.05$); however, for type 2, the odds ratio [OR] was 6.29 ($p < 0.001$), provided lactoferrin is present (data not shown).

The presence of syndesmophytes was independently associated with spinal radiographic progression and an odds ratio [OR] of 0.810 ($p < 0.001$), elevated levels of acute phase reactants (for the Erythrocyte Sedimentation Rate, OR of 0.810, $p < 0.9$; for C - reactive protein level OR of 1.948, $p < 0.9$) and lactoferrin (OR 0.267. $p = 0.012$) (Table 6).

Discussion

The number tests for the association between biomarkers and the behavior and phenotype of the inflammatory bowel disease (IBD) has significantly increased over the past few years; however, their role as predictors for EA has not yet been established, and even less so in mestizo populations such as the Venezuelan people [22].

Our analysis indicates that the most relevant variables contributing to the explanation of sacroiliitis are: Lactoferrin, ANCA and HLA B27 ($p < 0.09$). A variable that may be excluded because of its almost insignificant contribution is fecal Calprotectin. One of the frequent diagnostic difficulties is that of differentiating between mild to moderate cases, with varying underlaying causes for intestinal inflammatory processes of those that do not present with an organic disease, although in our study, most patients presented with high DAS28 and BASDAI scores.

There are conflicting opinions with regards to the vulnerability of biomarkers and the use of drugs (measurements in treated patients) [23-27], considering that all of our patients are already being treated with some type of drug, which may influence the measurement of the biomarker. Kohlo, et al. [28], showed that the use of glucocorticoids did not influence the calprotectin values; however, one year later, the Spanish work by Bonnin, et al. [29] found that the levels of Calprotectin decreased following the use of corticosteroids; in our study, most patients (69%) were receiving glucocorticoid therapy.

Table 4: Correlations among biomarkers.

			ESR	CRP	ANA	ANCA	LACTOFERRIN	CALPROTECTIN	ASCAIgA	ASCAIgG
Spearman's Rho	ESR (n	Coefficient	1.000	.157	-.080	.021	-.113	.005	-.054	-.025
		Sig. (Bil)		.321	.613	.894	.478	.973	.733	.876
	PCR	Coefficient	.157	1.000	-.072	-.167	.095	.079	.123	.091
		Sig. (Bil)	.321		.650	.291	.548	.618	.438	.567
	ANA	Coefficient	-.080	-.072	1.000	.146	-.059	.080	.070	-.028
		Sig. (Bil)	.613	.650		.355	.709	.614	.659	.860
	ANCA	Coefficient	.021	-.167	.146	1.000	.060	.055	.270	-.049
		Sig.(Bil)	.894	.291	.355		.706	.731	.084	.760
	LACTOFERRINA	Coefficient	-.113	.095	-.059	.060	1.000	.253	-.160	-.396**
		Sig.(Bil)	.478	.548	.709	.706		.106	.311	.009*
	CALPROTECTINA	Coefficient	.005	.079	.080	.055	.253	1.000	-.248	-.078
		Sig. (Bil)	.973	.618	.614	.731	.106	.	.114	.623
	ASCA IgA	Coefficient	-.054	.123	.070	.270	-.160	-.248	1.000	.097
		Sig.(Bil)	.733	.438	.659	.084	.311	.114	.	.541
	ASCA IgG	Coefficient	-.025	.091	-.028	-.049	-.396**	-.078	.097	1.000
		Sig. (bil)	.876	.567	.860	.760	.009	.623	.541	.
		N	42	42	42	42	42	42	42	42

**The correlation is significant at the 0.01 level (bilateral).

Table 5: Radiographic progression model.

Step	Chi square	gl	Sig.		
1	4.794	8	.779		
	Observed		Forecasted		
			Sacroiliitis		Correct percentage
			.00	1.00	
Step 1	Sacroiliitis	.00	11	10	52.4
		1.00	7	14	66.7
	Overall percentage				59.5

a. The cut point is .500

Table 6: Radiographic progression assessed through the presence of syndesmophytes.

	B	E.T.	Wald	gl	Sig.	Exp(B)
ESR	-0.211	0.674	0.098	1	0.755	0.81
CRP	0.667	1.049	0.404	1	0.525	1.948
ASCA IgA	-0.027	0.051	0.285	1	0.593	0.973
HLA B27	-0.508	0.889	0.327	1	0.568	0.602
Calprotectin	0.003	.004*	0.71	1	0.399	1.003
Lactoferrin	-1.321	1.159	1.299	1	0.254	0.267
Syndesmophyte	0.167	0.648	0.067	1	0.796	1.182

In the H-L model (Table 7) you may appreciate that the rise in ANCA from 0 to 1, with the rest of the variables remaining constant, results in a 1.948 fold increase in the odds ratio; however, the increase in HLA B27 from 0 to 1, with the other variables remaining constant, results in a drop in the odds ratio of 0.602 for Lactoferrin, an increase in Lactoferrin from 0 to 1, with the other variables remaining constant, resulting in a drop in the odds ratio of 0.267.

We now have markers available derived from several gut microbial species (antibodies against porin type C from the *Escherichia coli* outer membrane, antibodies against *Pseudomonas fluorescens*-associated I2 sequence, antibodies against flagellin, antibodies against chitobioside, laminaribioside, and mannobioside carbohydrates) which allow for new ways of classifying patients with IBD [30]. These markers may act as prognostic and behavioral indicators of the disease; furthermore, like in the case of ASCA and ANCA, the combined results lead to improved diagnostic certainty [31-34].

It should be highlighted however that correlation coefficients measure the relationships between the variables considered, keeping the other variables constant and should not be interpreted vis a third variable. Hence, in our prediction model, the variables Lactoferrin and ASCA IgG are considered a worse prognosis for the development of sacroiliitis.

An Italian study group found that ultrasound abnormalities in enthesis are present in a high proportion of patients with IBD, with no signs or clinical symptoms of SpA [36]. Out of the 81 patients, 71 (92.6%) presented almost a tendon disorder that included increased thickness, enthesophytosis, bursitis, and erosions. However, the power Doppler was only positive in 13/81 (16%) of the patients. Moreover, enthesopathy as identified by ultrasound, was not associated with the activity, the duration or the type of intestinal disease.

Notwithstanding the fact that our radiographic progression model (Table 5) resulted in a not very high value of 60%, it isn't neglectable either; the model is better able to identify the presence of sacroiliitis when it is indeed present, rather than not identifying the presence of sacroiliitis when in fact it is not present.

One of the downsides to be acknowledged with regards to this paper is the failure to contrast biomarkers against a control group, recognizing that several biomarkers such as ASCA and Lactoferrin may actually be present in other pathologies different from IBD; i.e., colon and rectal cancer, celiac disease, irritable colon and microscopic cholangitis [37-39].

Conclusion

The current diagnostic approach based on the clinic, endoscopy, histology, radiology and on biochemical criteria, provides a reliable diagnosis in most cases with IBD, as well as the differentiation among the different subtypes: however, many of these patients are not referred to the rheumatologist because their primary complaint is chronic diarrhea and many of the symptoms overlap with the gastrointestinal condition (arthralgias or enthesitis) [40-42]. Furthermore, the use of DC-ART and other biological therapies may suppress pain but not inflammation and the natural history of the disease, leading to the development of syndesmophytes and/or sacroiliitis which disable the patient for life [43,44]. The study of new biomarkers as an additional tool for the clinician will help us to differentiate those patients that should be referred to the rheumatologist and decide in which cases should other therapies be associated to avoid the development of enteropathic arthritis (EnA).

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