Original article

Evaluation of the concordance between biological markers and clinical activity in inflammatory bowel disease

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A R T I C L E   I N F O

Article history:
Received 15 June 2013
Accepted 5 September 2013

Keywords:
Crohn’s disease
Ulcerative colitis
Serological biomarkers
Clinical activity
C reactive protein

A B S T R A C T

Background and objectives: Endoscopy is the gold standard to assess disease severity in inflammatory bowel disease, although it is an invasive procedure. Clinical activity and biological markers have been routinely used to determine disease activity in a non-invasive manner. The aim of this study was to determine concordance between common biological markers (C reactive protein, orosomucoid, erythrocyte sedimentation rate, fibrinogen, platelets, leukocytes, neutrophils and haemoglobin) and clinical activity in inflammatory bowel disease.

Patients and method: Consecutive patients with inflammatory bowel disease were included. Clinical activity was evaluated according to the Harvey–Bradshaw index in Crohn’s disease and to the partial Mayo score in ulcerative colitis. Serum concentrations of the different biomarkers were analysed. Concordance between clinical activity and elevation of the serological biomarkers was determined using the kapp statistic.

Results: In total, 350 patients were included (median age 46 years, Crohn’s disease 59%). Eleven percent of patients had clinical activity. Crohn’s disease patients had mild clinical activity in 44% of cases, moderate disease in 44% and only 12% of patients had severe clinical activity. In ulcerative colitis, patients had mild, moderate and severe clinical activity in 50%, 42% and 8% of cases, respectively. None of the biomarkers included had an acceptable concordance with clinical activity (kappa statistic ≤ 0.30).

Conclusions: Concordance between serological biomarkers and clinical activity in inflammatory bowel disease is remarkably low.

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Concordancia entre la actividad clínica y los marcadores biológicos en la enfermedad inflamatoria intestinal

R E S U M E N

Fundamento y objetivos: La ileocolonoscopía es el patrón oro para determinar el grado de actividad de la enfermedad inflamatoria intestinal. Sin embargo, es una técnica invasiva. La actividad clínica y los marcadores biológicos se han empleado como indicadores indirectos para determinar, de forma no invasiva, el grado de actividad inflamatoria. El objetivo de este estudio fue determinar la concordancia entre los marcadores biológicos séricos más utilizados (proteína C reactiva, orosomucoido, velocidad de sedimentación globular, fibrinógeno, plaquetas, leucocitos, neutrófilos, hemoglobina) y la actividad clínica de la enfermedad inflamatoria intestinal.

Pacientes y método: Se incluyeron prospectivamente pacientes consecutivos en los que se evaluó la actividad clínica medida mediante el índice de Harvey–Bradshaw en la enfermedad de Crohn, y mediante el índice de Mayo parcial en la colitis ulcerosa. Se cuantificaron los valores de los diversos marcadores biológicos. Se determinó la concordancia de la actividad clínica con la elevación de los marcadores biológicos mediante el estadístico kappa.

Palabras clave:
Enfermedad de Crohn
Colitis ulcerosa
Marcadores biológicos
Actividad clínica
Proteína C reactiva

* Please cite this article as: Miranda García P, Chaparro M, Gisbert JP. Concordancia entre la actividad clínica y los marcadores biológicos en la enfermedad inflamatoria intestinal. Med Clin (Barc). 2015;144:9–13.

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Results: Se incluyeron 350 pacientes (edad media 46 años, enfermedad de Crohn 59%). El 11% presentaba actividad clínica. De los pacientes con enfermedad de Crohn, el 44% tenía un brote leve, un 44% un brote moderado y un 12% un brote grave. Los pacientes con colitis ulcerosa presentaban actividad leve, moderada y grave en un 50, 42 y 8% de los casos, respectivamente. Ninguno de los marcadores biológicos estudiados se correlacionó aceptablemente con la actividad clínica (índices kappa ≤ 0,30 en todos los casos).

Conclusions: La concordancia de los marcadores biológicos con la actividad clínica de la enfermedad inflamatoria intestinal es notablemente baja.

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Introduction

Both Crohn’s disease (CD) and ulcerative colitis (UC) present a series of non-specific symptoms affecting mainly the gastrointestinal tract, such as abdominal pain or diarrhoea; patients can also have dermatologic, ocular or musculoskeletal manifestations, among others.1 Such symptoms may or may not be related to the inflammatory bowel disease (IBD), and may become an obstacle in assessing the rate of activity of IBD. The therapeutic decision-making should be based on the presence or absence of bowel inflammation.

Currently, the gold standard to establish the presence of IBD activity are the findings from an ileocolonoscopy.2 Unfortunately this is an expensive and invasive technique, with potential risks for the patient and sometimes of limited access. This is the reason why, for many years now, serological biological markers are used as indirect indicators to monitor IBD activity.3,4 Most of these markers are non-specific acute phase reactants, which can be elevated in extra-digestive processes; but they have the advantage of being accessible and cheap, and therefore widely used.5 However, there are few studies which have simultaneously analyzed the usefulness of these biological markers in a wide population of patients with IBD.

The purpose of our study was to assess the concordance among the different biological markers most widely used in the monitoring of IBD (C-reactive protein [CRP], orosomucoid, erythrocyte sedimentation rate [ESR], fibrinogen, platelets, leukocytes, neutrophils, haemoglobin) and the clinical activity inherent to the disease.

Data collection: clinical activity and biological markers

During the interview of the physician with the patient, the current presence and rate of clinical activity was established, based on the partial Mayo score (PMS) (Table 1) for patients with UC and the Harvey–Bradshaw index (HBI) (Table 2) for patients with CD. Patients had been subject to analytical determinations from 1 to 7 days prior to the consultation, and therefore the clinical and analytical data (CRP, orosomucoid, ESR, fibrinogen, platelets, leukocytes, neutrophils, haemoglobin) were registered prospectively during the interview with the patient. Biological markers were considered altered if they were above the higher limit of normal lab

Patients and method

Patients

A prospective and observational study was carried out, including consecutive patients who attended our hospital’s IBD Unit from January 2010 through June, 2011. The study was assessed and accepted by our centre’s Ethics’ Committee. The Montreal classification was used to define the characteristics of CD and the location of UC.

Inclusion criteria

(1) CD or UC diagnosis (established based on standard clinical, radiological, histological and endoscopic criteria).
(2) Consecutive patients who attended IBD clinics at our hospital from January 2010 to June 2011.

Exclusion criteria

(1) Absence of analytical determinations in the review.
(2) Patient’s refusal to participate in the study.

Table 1
Partial Mayo score to determine clinical activity in patients with ulcerative colitis.

| Frequency of bowel movement (subscore from 0 to 3): | 0 = regular number of bowel movements of the patient per day | 1 = 1–2 more bowel movements than usual per day | 2 = 3–4 more bowel movements than usual per day | 3 = 5 or more bowel movements than usual per day |
| Rectal haemorrhage (subscore from 0 to 3): | 0 = no blood observed | 1 = traces of blood in the faeces less than half of the times | 2 = evident blood in the faeces most of the time | 3 = only blood comes out |
| Global assessment by the physician (subscore from 0 to 3): | 0 = normal | 1 = mild disease | 2 = moderate disease | 3 = severe disease |

Table 2
Harvey–Bradshaw Index to determine clinical activity in Crohn’s disease.

| General condition | 0 = Very good | 1 = Regular | 2 = Bad | 3 = “Terrible” |
| Abdominal pain | 0 = None | 1 = Light | 2 = Moderate | 3 = Intense |
| Number of liquid stools per day | 0 = One point for each liquid stool |
| Abdominal mass | 0 = None | 1 = Doubtful | 2 = Defined | 3 = Defined and painful |
| Other related symptoms (one point for each complication) | Arthritis | Uveitis | Erythema nodosum/pyoderma/mouth aphthous ulcers | Fistula fissure/perianal abscess | Other fistulas |
values: CRP > 0.08 mg/l; ESR > 20 mm/h; orosomucoid > 125 mg/dl; fibrinogen > 500 mg/dl; leucocytes > 12,000/mm³; neutrophils > 7500/mm³; platelets > 400,000/mm³; haemoglobin <12 g/dl in women and <13 g/dl in men. A result of HBI ≤ 4 points and IMP of 0 points was considered as an absence of clinical activity; a result of HBI of 5 points and IMP between 1 and 3 points was considered a mild flare; an a result of HBI between 6 and 12 and an IMP between 4 and 6 points was considered a moderate flare; whereas a result of HBI > 12 points and IMP > 6 points was considered a severe flare.

### Statistical analysis

Quantitative variables were expressed as mean and standard deviation, or median and interquartile range, depending on whether they adjusted to a normal distribution or not. Quantitative variables were compared using the Student’s t test or a non-parametric test in the case of variables that did not adjust to a normal distribution.

The kappa statistic (and its standard error) was determined to establish the degree of concordance between the presence of clinical activity of the IBD and the rising of each biological marker above the normal lab value. The interpretation of the results obtained when calculating the kappa statistic was based on the Landis and Koch classification. To perform the statistical analysis, the SPSS® 15.0 statistical package was used.

### Results

350 patients were included, and the average age was 46 years (range from 17 to 91 years). Table 3 presents a description of the characteristics of the patients of the study.

With regard to the location of the disease, 20 of patients with UC presented proctitis, 45% left-sided colitis and 35% suffered from pancolitis. The most frequent location for CD was ileocolic (43%), followed by an exclusive ileal location (29%).

11% of patients showed IBD clinical activity. Eighteen patients with UC showed activity. The mean IMP was 4.2 points (range of 2–9), where 50% of patients had mild activity, 42% had moderate activity and 8% had severe activity. The HBI mean was 7 points (range of 5–13) for the 22 patients with clinical activity of CD: 44% had a mild flare, another 44% had a moderate flare, and 12% had a severe flare, according to the HBI.

When comparing the means for biological markers between the patients with and without clinical activity, we obtained the results displayed in Tables 4 and 5. In most of the biological markers assessed, the means were significantly higher in patients with clinical activity than in those in remission.

### Table 3

**Characteristics of patients included in the study (No. = 350).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (standard deviation), years</td>
<td>46 (15)</td>
</tr>
<tr>
<td>Crohn’s disease/ulcerative colitis</td>
<td>206/144 (59/41)</td>
</tr>
<tr>
<td>Male</td>
<td>182 (48)</td>
</tr>
<tr>
<td>Location of ulcerative colitis</td>
<td>Proctitis: 29 (20)</td>
</tr>
<tr>
<td>Pattern (Crohn’s disease)</td>
<td>Inflammatory: 115 (56)</td>
</tr>
<tr>
<td>Presence of clinical activity</td>
<td>40 (11)</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>49 (14)</td>
</tr>
</tbody>
</table>

Data expressed as No. (%), except were stated otherwise.

### Table 4

**Values of the different biological markers in patients with and without clinical activity of Crohn’s disease.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Patients without clinical activity</th>
<th>Patients with clinical activity</th>
<th>p (Student’s t test)</th>
<th>Median</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>0.68 ± 1.9</td>
<td>1.82 ± 2.9</td>
<td>0.01</td>
<td>0.2</td>
<td>17.00</td>
<td>0.00</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>18 ± 16</td>
<td>25 ± 22</td>
<td>0.1</td>
<td>14</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>Orosomucoid (mg/dl)</td>
<td>98 ± 40</td>
<td>118 ± 49</td>
<td>0.08</td>
<td>92</td>
<td>301</td>
<td>26</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>404 ± 97</td>
<td>469 ± 18</td>
<td>0.01</td>
<td>399</td>
<td>731</td>
<td>200</td>
</tr>
<tr>
<td>Leukocytes (ml)</td>
<td>7050 ± 2403</td>
<td>8420 ± 4370</td>
<td>0.04</td>
<td>6780</td>
<td>22,130</td>
<td>1390</td>
</tr>
<tr>
<td>Neutrophils (ml)</td>
<td>4290 ± 1774</td>
<td>5664 ± 3884</td>
<td>0.01</td>
<td>4060</td>
<td>17,000</td>
<td>819</td>
</tr>
<tr>
<td>Platelets (ml)</td>
<td>263 ± 90 × 103</td>
<td>315 ± 102 × 103</td>
<td>0.02</td>
<td>252,000</td>
<td>782,000</td>
<td>105,000</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.8 ± 1.6</td>
<td>12.3 ± 1.3</td>
<td>0.001</td>
<td>13.5</td>
<td>19</td>
<td>9</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. Data expressed as a mean ± standard deviation.

### Table 5

**Values of the different biological markers in patients with and without clinical activity of ulcerative colitis.**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Patients without clinical activity</th>
<th>Patients with clinical activity</th>
<th>p (Student’s t test)</th>
<th>Median</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/l)</td>
<td>0.50 ± 1.6</td>
<td>0.59 ± 0.9</td>
<td>0.7</td>
<td>0.2</td>
<td>16.00</td>
<td>0.0</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>14 ± 12</td>
<td>23 ± 16</td>
<td>0.01</td>
<td>13</td>
<td>73</td>
<td>1</td>
</tr>
<tr>
<td>Orosomucoid (mg/dl)</td>
<td>92 ± 27</td>
<td>108 ± 34</td>
<td>0.02</td>
<td>90</td>
<td>251</td>
<td>46</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>382 ± 80</td>
<td>441 ± 94</td>
<td>0.02</td>
<td>379</td>
<td>713</td>
<td>218</td>
</tr>
<tr>
<td>Leukocytes (ml)</td>
<td>6528 ± 1851</td>
<td>6812 ± 3007</td>
<td>0.6</td>
<td>6440</td>
<td>16,500</td>
<td>2050</td>
</tr>
<tr>
<td>Neutrophils (ml)</td>
<td>3864 ± 1348</td>
<td>4232 ± 2555</td>
<td>0.3</td>
<td>3580</td>
<td>12,450</td>
<td>1020</td>
</tr>
<tr>
<td>Platelets (ml)</td>
<td>235 ± 60 × 103</td>
<td>287 ± 122 × 103</td>
<td>0.004</td>
<td>235,000</td>
<td>717,000</td>
<td>107,000</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14.2 ± 1.5</td>
<td>13.4 ± 2.2</td>
<td>0.04</td>
<td>14</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. Data expressed as a mean ± standard deviation.
In Tables 6 and 7 we can see the concordance of each biological marker with the clinical activity in CD and UC, respectively, measured with the kappa coefficient and its related standard error. In the case of UC, markers with the highest kappa coefficient were haemoglobin, CRP and oesosomucoid (k of 0.28, 0.24 and 0.21, respectively). In CD, markers with the highest results were neutrophils (k = 0.25), leucocytes (k = 0.22) and haemoglobin (k = 0.22).

**Discussion**

The results of this study show that, globally, the concordance between the biological markers assessed and the clinical activity of IBD is low, both in patients with UC and those with CD, since the kappa index was in no case above 0.3.

It is possible that different results in the concordance between clinical and biological markers would be obtained if we choose the highest cut-off points to consider there is clinical activity. However, in practice, we need to identify all patients with potential IBD activity, and therefore we need sensitive diagnostic methods; that is to say, we have to suspect clinical activity in the presence of mild symptoms, even if these are not very specific. These cut-off points were chosen to define clinical activity based on prior studies which used these indexes to determine the degree of clinical activity.4, 3

In CD, the concentration of neutrophils and leucocytes and the haemoglobin levels were the markers with the best concordance with clinical activity, reaching kappa coefficient figures close to 0.25, which implies only a discrete concordance. The rest of the markers resulted in kappa coefficients below 0.20, evidencing insignificant concordance. In the case of UC, the results were similar, where haemoglobin level was the marker with the highest kappa coefficient (0.28).

The concordance between CRP and clinical activity in our patients with UC was discrete (kappa coefficient = 0.24). However, this marker has been proposed in other studies as a good predictor of the need for colectomy in patients with severe flares of UC9, 10 and has shown a good correlation with clinical activity if the UC is not limited to the rectum and if the activity is severe.11, 12 It is possible that these results are not confirmed due to the relatively high number of proctitis included (20%), where the systemic inflammatory response is not enough to elevate the biological markers. On the other hand, there are few patients in our sample with severe UC activity. However, other authors have observed, like we did, that CRP does not rise significantly in patients with active UC.13–15 These last results in UC may be explained based on the fact that, in theory, the inflammation in UC is limited to the mucosa, which would not generate sufficient inflammatory mediators to induce an increase in the synthesis of CRP.16

The results of CRP in our patients with CD were more surprising, since this biological marker had an insignificant correlation with clinical activity (k = 0.18). Results similar to ours have been described in patients with ileal disease and stenosing CD.12 However, during the last years it has been considered that CRP is more useful to estimate the activity of CD than the activity of UC.14, 17 In this sense, CRP has shown a good correlation in some studies with endoscopic activity in patients with CD,18 although other studies show contradictory data.19–23

Based on the markers studied, it is worth noting that haemoglobin was the parameter that best correlates with the clinical activity in patients with UC. The presence of anaemia has been associated to a worse diagnosis in patients with UC, and a higher rate of colectomy.24 In any case, the kappa coefficient in our study was not even above 0.30.

On the other hand, ESR obtained an insignificant concordance with clinical activity, both in patients with UC (k = 0.16) and with CD (k = 0.08). The same happened with the rest of the markers studied.

The low concordance between the biological markers evaluated and clinical activity may be due to the fact that several symptoms attributed to IBD, such as abdominal pain, fatigue or diarrhea, are not always secondary to inflammatory activity, but may be the consequence of intercurrent processes or concomitant functional disease.25 It seems to be demonstrated that there is a poor correlation between clinical remission (evaluated by the Crohn Disease Activity Index) and the endoscopic improvement (assessed using the Crohn’s Disease Endoscopic Index of Severity) in patients with CD treated with corticoids.26 Likewise, there may be inflammation and lesions in the mucosa that do not translate into symptoms and may, however, produce an inflammatory reaction evidenced by the measurement of serum biological markers.

Currently, the purpose of the treatment of IBD is to control inflammatory activity in the gastrointestinal tract, since mucosal healing is the factor that has most consistently been related to a better evolution of patients, by modifying the natural history of the disease, decreasing hospitalisation rates and surgery both in CD and UC.27–31 Also, the damage caused by persistent inflammation of the mucosa can cause irreversible anatomical and functional changes. Therefore, it has been said that to evaluate the response to treatments and make clinical decisions an objective determination of the presence of active inflammation in the gastrointestinal tract is necessary, and that a therapeutic management based solely on the presence or absence of symptoms is not suitable,32 as evidenced by our results. However, we must be cautious when interpreting the results of this study, because the kappa value is affected by the prevalence of the feature studied and in our sample the prevalence of activity was low. Another limitation of our study is that it has a cross-sectional design, and therefore we cannot infer if the clinical activity or the biological markers can have other roles in the management of the disease, such as predicting its course or evaluating a potential response to treatment. On the other hand, given the limitations of endoscopy already discussed, we need to have biological markers to estimate indirectly, but objectively, the activity of IBD and that closely correlate with the degree of intestinal inflammation.3, 33

In conclusion, the concordance between the serum biological markers evaluated and the clinical activity of IBD is low; however, in order to know the diagnostic accuracy of these biological markers,
we need studies to determine their correlation to the inflammatory activity measured using the gold standard: ileocolonoscopy.

Conflict of interests

The authors declare that there are no conflicts of interest.

References


