RESEARCH LETTER

A simple index to predict the efficiency of adalimumab treatment in Crohn disease with a limited duration of therapy

Marcin Sochal¹, Monika Krzywdzińska², Agata Gabryelska¹, Renata Talar-Wojnarowska², Piotr Białasiewicz¹, Ewa Małecka-Panas²

1 Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, Łódź, Poland

2 Department of Digestive Tract Diseases, Medical University of Lodz, Łódź, Poland

Introduction Anti–tumor necrosis factor- α monoclonal antibody (anti-TNF- α) therapy in patients with severe Crohn disease (CD) has high efficacy and is associated with clinical improvement and a lower number of surgical interventions.^{1,2} However, there is a group of patients who show an unsatisfactory response to biologic therapy.

Most treatment programs use anti-TNF- α therapy to achieve deep remission. Part of therapeutic failures may be due to severe adverse effects or high treatment costs, which lead to limited therapy duration. The Polish insurer used to refund adalimumab therapy for 1 year. Therefore, it is interesting to examine the predictive value of selected clinical and laboratory parameters regarding the efficacy of time-limited therapy. Blood cell count is a cheap, widely ordered test, and numerous studies have pointed to the relevant role played by platelets in the immune system, apart from contributing to hemostasis. Mean platelet volume (MPV) is measured by automated analyzers and used to assess thrombocytopenia.³

Several studies have related MPV to the severity of autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.³ Moreover, decreased MPV is observed in thromboembolic disorders, the risk of which is increased in CD.^{4,5}

Clinical factors also considerably influence the course of CD. Legué et al⁶ showed that 53.3% of patients with fistulas had a relapse after a median follow-up time of 62 months. Another study has shown that in patients treated with infliximab who had no history of surgery, the remission time was longer than in those who underwent surgery in the past.⁷ However, there has been no similar study assessing the prognostic value of these factors in the efficacy evaluation of anti-TNF- α therapy limited to 1 year.

Therefore, in this study, we aimed to develop a simple index based on blood count parameters and clinical variables to predict the efficacy of limited, 1-year adalimumab therapy.

Patients and methods This retrospective study included 47 patients with CD who received adalimumab for 52 weeks. The inclusion criteria for biologic treatment were as follows: Crohn Disease Activity Index above 300, no response or intolerance and/or contraindications to conventional treatment with glucocorticosteroids and/or immunosuppressants, or persistent fistulas. The biologic treatment consisted of 12-week induction therapy and 40-week maintenance therapy; adalimumab at a dose of 160 mg was administered subcutaneously at the beginning of the therapy, at 80 mg after 2 weeks, and then at 40 mg every 2 weeks.

Venous blood was drawn from patients before and after 12-week induction therapy and the following parameters were analyzed: white blood cell (WBC) count, platelet count, and MPV. Clinical data were collected, with a particular emphasis on the history of CD complications (ie, fistulas, abscesses, fissures, intestinal stenosis, and obstruction). Six months after the end of the treatment, data on clinical exacerbation of CD regarding surgical therapy and glucocorticoid use or biologic retreatment during this period were obtained from patients' medical records.

We developed an index based on selected blood count parameters and clinical variables related to the course of the disease. Only variables with significant odds ratios (ORs) were included in the index and weights were allocated for each parameter based on the OR value.

Marcin Sochal, MD, Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, ul. Mazowiecka 6/8, 92-215 Łódź, Poland, phone: +48426781800, email: sochalmar@gmail.com Received: May 20, 2020. Revision accepted: June 30, 2020. Published online: July 9, 2020. Pol Arch Intern Med. 2020; Ja0 (10): 910-912 doi: 10.20452/pamw.15507 Copyright by the Author(s), 2020

Correspondence to:

Parameter	Cutoff point	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	P value
MPV, fl	<10.4	0.52	0.88	0.8	0.66	0.71 (0.56–0.86)	0.006
WBC, $\times 10^{9}/I$	>7.9	0.83	0.63	0.68	0.69	0.73 (0.58–0.88)	0.003
Index value	<2	0.35	0.97	0.89	0.61	0.88 (0.79–0.98)	< 0.001
-	<3	0.7	0.92	0.89	0.76		
	<4	0.83	0.79	0.79	0.83		
	<5	0.83	0.75	0.76	0.82		
-	<6	0.96	0.58	0.69	0.93		

TABLE 1 The diagnostic value of selected cutoff points of mean platelet volume, white blood cell count, and the proposed index

Abbreviations: AUC, area under the receiver operating characteristic curve; MPV, mean platelet volume; NPV, negative predictive value, PPV, positive predictive value; WBC, white blood cells

The study was approved by the local bioethics committee (RNN/372/18/KE). Due to the retrospective design, written informed consent to participate in the study was not applicable. Statistical analysis was performed using the Statistica 13.1 software for Windows (StatSoft, Inc., Tulsa, Oklahoma, United States). The distribution of variables was assessed using the Shapiro–Wilk test. The Fisher exact test was used for comparison of nominal variables, and the Mann–Whitney test for quantitative variables with distribution other than normal. Quantitative variables were expressed as median (interquartile range). Odds ratios and 95% CIs were calculated. Odds ratios were estimated using logistic regression for continuous variables. The sensitivity and specificity of the prognostic scale were determined using receiver operating characteristic curves and the area under the curve (AUC) was calculated. The Hanley and Hajian-Tilaki method was used to compare AUCs. A P value less than 0.05 was considered significant.

Results We analyzed the data of 47 patients who completed induction therapy and received adalimumab for 52 weeks. At 18-month follow-up, 24 patients (51.1%) had a relapse.

No differences in the values of WBC count, platelet count, and MPV measured before therapy were observed between patients who achieved long-term remission and those who relapsed.

Patients who maintained long-term remission after 1-year therapy had increased MPV and a decreased WBC count compared with those who relapsed (measurement performed after 12 weeks of the therapy). No such differences were noted for the platelet count (Supplementary material, *Table S1*).

To determine the cutoff points for MPV and WBC count at therapy week 12, which would identify patients at increased risk of exacerbation, the Youden index of the receiver operating characteristic curve was used with the following results: $7.9 \times 10^9/l$ for WBC count and 10.4 fl for MPV (TABLE 1).

Fistulas were more frequently present at the beginning of the therapy in patients in whom disease exacerbation was observed as compared with patients with sustained remission. Similarly, the history of intestinal complications and previous abdominal surgery were associated with exacerbation (Supplementary material, *Table S1*).

Based on ORs, the following items were selected and assigned weights to develop a simple predictive index: the presence of fistulas (OR, 10.5; 2 points), previous abdominal surgery (OR, 5.6; 1 point), CD complications (OR, 10.8; 2 points), MPV <10.4 fl (OR, 7.6; 1 point), and WBC count >7.9 × 10⁹/l (OR, 6; 1 point). Obtaining less than 3 points identified 89% of patients who maintained 18-month remission (TABLE 1). There was a significant difference in the AUC for the index and MPV (P = 0.03), the index and WBC count (P = 0.03), yet not for MPV and WBC count (P = 0.86).

Discussion Numerous studies have investigated the usefulness of blood cell count in predicting the efficacy of biologic treatment. Similar to the study by Sobolewska et al,⁸ we demonstrated that a lower WBC count was a predictor of successful anti-TNF-α therapy. That study examined the predictive value of MPV for maintaining response to treatment after infliximab induction therapy in CD. Higher MPV was observed both at the beginning of the therapy and after 12 weeks in patients with remission compared with those who relapsed.8 In that study, the sensitivity and specificity of MPV were similar to those observed in our study. However, our results indicate that the predictive value of MPV is similar to that of WBC count.

The obtained results can be explained by the fact that platelets are also regarded as regulators of immune responses. Numerous receptors on their surface are involved not only in regulating hemostasis but also in immunological reactions. Their role in activating and suppressing the immune system remains unclear, but they seem to exert a dual function.³ Platelets store and release many mediators, including serotonin—a hormone that is part of the gut–brain axis. A recent study showed that the serum level of serotonin was associated with the endoscopic severity of inflammatory bowel diseases.^{3,9} Besides, TNF- α affects hematopoiesis, but its role is complex and has not been fully understood. It also has procoagulant

properties and some studies reported thrombocytopenia after anti-TNF- α therapy.¹⁰

Interestingly, small platelet size correlated with cardiovascular risk, which is also higher in patients with CD.^{5,11} Our study results show that patients who maintain lower MPV following the induction therapy quickly relapse. Therefore, especially in these patients, a longer therapy should be considered. This can improve the quality of life of patients while reducing treatment costs, because, as we have shown elsewhere,² 38.5% of patients after a year of therapy re-enter the induction therapy within half a year. This results in higher costs of treatment than those of continuing maintenance treatment.

We also identified some clinical variables that can help to predict the effects of biologic therapy and our results are similar to those obtained in other studies.^{6,7}

In this study, we presented a simple scale that may identify patients at increased risk of relapse after response to time-limited adalimumab therapy. The index is characterized by a high specificity and a positive predictive value, yet has a low sensitivity. It satisfactorily identified patients who relapsed within 6 months after a 1-year therapy. Such an index seems to be particularly relevant for therapeutic programs. Therefore, prolonged therapy should be considered in patients with lower chance of achieving long-term remission. In a multicenter study,¹² a 7-point clinical--radiological scale related to response to adalimumab treatment was constructed, including the presence of fistulas as a negative predictor. A total of 89% of patients who scored 4 points and more maintained therapeutic success.¹² However, that scale does not apply to patients treated for a limited period of time.

Our study showed that high MPV and low WBC count together with selected clinical variables at week 12 of adalimumab therapy may predict long-term remission in patients with CD. The addition of selected clinical variables provided a more specific tool for estimating long-term remission. This index should be prospectively validated in a larger group of patients. It can be particularly useful in countries with limited access to modern therapies and may further help to reduce the cost of treating patients with CD while maintaining therapy efficacy at the same time.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT EMP and MS provided the overall concept and framework of the manuscript. MS, MK, and AG collected the data. MS and PB analyzed the data. MS wrote the paper. RTW, PB, AG, and EMP revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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