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Folia Medica 66(2):188-195
DOI: 10.3897/folmed.66.e114887

Original Article

Prognostic Models of Drug-Induced Neutralizing Antibody Formation in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis Treated with TNF-α Blockers

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Received: 30 Oct 2023 ♦ **Accepted:** 23 Feb 2024 ♦ **Published:** 30 Apr 2024

Citation: Kraev K, Hristov B, Uchikov P, Kraeva M, Geneva-Popova M, Popova S, Basheva-Kraeva Y, Stoyanova NS, Mitkova-Hristova V. Prognostic models of drug-induced neutralizing antibody formation in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis treated with TNF-α blockers. Folia Med (Plovdiv) 2024;66(2):188-195. doi: 10.3897/folmed.66.e114887.

Abstract

Aim: This study aimed to construct prognostic mathematical models utilizing multifactorial regression analysis to assess the risk of developing drug-induced neutralizing antibodies in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis treated with tumor necrosis factor alpha blockers.

Materials and methods: Over a four-year period, we enrolled 213 patients in this study and divided them into three groups: the rheumatoid arthritis group (n=121), the ankylosing spondylitis group (n=50), and the psoriatic arthritis group (n=42). The study included also a group of healthy controls consisting of 31 healthy subjects who matched the patient groups in age, sex, body mass index, and conditions typical for rheumatology patients. Prognostic mathematical models based on statistically significant factors determined through univariate correlation and regression analyses incorporated patient medical history and serological and immunological data.

Results: The study encompassed all 213 patients and 31 healthy controls. Data analysis was conducted at 12 and 24 months after commencing treatment. During this follow-up, the patients exhibited the highest percentage of antidrug antibodies. At 6 months, 6.57% of patients had confirmed neutralizing antibodies, which increased to 12.69% at 12 months and 17.72% at 24 months. Multivariate logistic regression analysis revealed that factors such as age over 55 years, excess weight, smoking, and absence of methotrexate treatment at a dose less than 7.5 mg per week had the highest predictive value.

Conclusions: Investigating clinical and biological markers with predictive value for individual patients' therapeutic responses is a complex task. This complexity arises from the interplay of at least three distinct parameters: the patient's disease state, drug bioavailability, and pathophysiological changes within the patient's body, all of which are influenced by various factors.

Keywords

anti-drug antibodies, prognostic model

INTRODUCTION

The increasing prevalence of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) has led to a growing reliance on tumor necrosis factor alpha (TNF-α) blockers for the management of these conditions. While these drugs have demonstrated efficacy in ameliorating symptoms and improving quality of life for patients, the emergence of drug-induced neutralizing antibodies poses a significant concern. These antibodies can compromise the effectiveness of TNF-α blockers, leading to diminished therapeutic outcomes and potential complications in patients undergoing treatment.

In light of this, there is a pressing need to develop robust prognostic models that can assess the risk of patients developing drug-induced neutralizing antibodies. To address this concern, our study employed multifactorial regression analysis to construct mathematical models for evaluating the risk in patients with RA, PsA, and AS. This involves an in-depth examination of various demographic, clinical, and immunological factors, identified through univariate correlation and regression analyses, to ensure the models are based on statistically significant variables.[1-3]

Existing literature underscores the importance of considering patient medical history, serological, and immunological data in constructing predictive models for drug-induced neutralizing antibodies.[4] Despite the acknowledged significance of these factors, there remains a dearth of comprehensive studies that integrate them into a unified prognostic framework. Our research seeks to bridge this gap by providing a thorough exploration of the interplay between demographic, clinical, and immunological factors, emphasizing their collective impact on the development of neutralizing antibodies in patients treated with TNF-α blockers.

AIM

This study aims to contribute not only prognostic models but also a deeper understanding of the intricate relationships between patient characteristics and the risk of developing neutralizing antibodies. By addressing this gap in the literature, we strive to enhance the precision of risk assessment and, subsequently, the effectiveness of therapeutic interventions in patients undergoing TNF-α blocker treatment.

MATERIALS AND METHODS

This prospective, longitudinal, open-label study spanned a four-year period, involving a comprehensive assessment of 213 patients diagnosed with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The study also included a control group consisting of 31 healthy individuals. The patient groups were further divided into two categories based on the type of biological agent used: adalimumab and etanercept.

A cross-sectional, multicenter observational approach was employed for data collection. After obtaining informed consent, patients were interviewed, examined, and their information was collected and entered into files for subsequent statistical analysis. Self-assessment questionnaires were voluntarily completed by patients, and blood samples were taken for the assessment of cytokines (TNF-α and IL-6) and the detection of drug-induced neutralizing antibodies. Some patients, particularly those treated with adalimumab, were additionally tested for drug bioavailability six months after treatment initiation.

Participant groups

The patients included 121 with RA, 50 with AS, and 42 with PsA, while the control group comprised 31 healthy individuals. The demographic characteristics, disease-specific details, and medication information for each group were meticulously recorded **(Table 1)**.

These categorizations were implemented to allow a comprehensive analysis of the impact of demographic, clinical, and immunological factors on the development of

Table 1. Number of individuals monitored – patients and healthy controls by number, age, sex, underlying disease, and disease duration (x±Sx)

Indicators	Patients treated with adalimumab	Patients treated with etanercept	Healthy control individuals
Number	121	92	31
Main disease, number of patients			
Rheumatoid arthritis	79	42	
Ankylosing spondylitis	16	34	
Psoriatic arthritis	26	16	
Age, years	49.8±10.8	45.6±13.4	48.7±2.2
Sex			
Men, n (%)	43 (35.54%)	47 (51.08%)	15 (48.28%)
Women, n (%)	78 (64.46%)	45 (48.02%)	16 (51.62%)

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drug-induced neutralizing antibodies in patients treated with TNF-α blockers. The rationale for grouping patients based on both disease type and medication is to account for potential variations in treatment response and antibody development among different rheumatological conditions and specific medications.

Hypotheses

The null hypothesis (H0) posited that the presence of neutralizing antibodies to TNF-α blockers used in the treatment of severe forms of RA, AS, and PsA is clinically relevant, affecting the course of the disease. Conversely, the alternative hypothesis (H1) proposed that these antibodies do not influence the disease's progression.

Inclusion and exclusion criteria

Patients meeting the established diagnostic and classification criteria for RA, PsA, and AS and undergoing treatment with adalimumab or etanercept were included. Exclusion criteria were carefully defined to ensure the selection of eligible participants.

Study procedures

This study utilized a variety of clinical and laboratory methods **(Table 2)**, including comprehensive medical history and examination, pain assessment using a visual analogue scale (VAS), disease activity evaluations specific to each condition, and assessment tools such as Disease Activity Score in 28 joints (DAS-28), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Health Assessment Questionnaire – Disability Index (HAQ-DI).

Table 2. Clinical and laboratory studies performed during patient visits

Procedure	0 mos	6 mos	12 mos	24 mos
Medical history	•	•	•	•
Physical examination	•	•	•	•
Pain assessment (VAS)	•	•	•	•
Disease activity indices	•	•	•	•
CRP	•	•	•	•
ESR	•	•	•	•
Serum levels of drug induced neutralizing antibodies	•	•	•	•
Bioavailability of the drug		•	•	•

Self-assessment questionnaires

Patients voluntarily filled out two key self-assessment questionnaires to provide information about their subjective experiences and perceptions of their rheumatological conditions.

Visual Analogue Scale (VAS)

Patients used a VAS to subjectively indicate their pain intensity at the time of examination. This scale allowed patients to express their pain levels on a continuous scale, providing valuable information on pain perception.

Health Assessment Questionnaire Disability Index (HAQ-DI)

HAQ-DI was employed to assess patients' quality of life by examining their ability to perform daily activities. Higher HAQ-DI values indicated greater disability, allowing for an evaluation of the impact of rheumatological conditions on daily functioning.

Laboratory investigations

These included:

Complete blood count (CBC): assessing the number and types of blood cells to evaluate general health and detect abnormalities.

Erythrocyte sedimentation rate (ESR): a non-specific measure of inflammation, indicating the presence of an inflammatory condition.

C-reactive protein (CRP): another marker of inflammation often used to monitor disease activity.

Cytokine assays: TNF-α and IL-6: these were assayed using ELISA methodology with specific kits to measure the levels of these proinflammatory cytokines.

Determination of neutralizing antibodies

Antidrug antibodies

Assayed for etanercept (Enbrel) and adalimumab (Humira) using ELISA with Immundiagnostik kits.

Determination of drug bioavailability

Assessed in two independent laboratories using ELISA methodology from Immundiagnostik.

Observation parameters

Patient visits at 0, 6, 12, and 24 months included a thorough examination of medical history, physical examination, pain assessment, disease activity indices, and relevant laboratory tests.

Study locations

The research was conducted at the Department of Propaedeutics of Internal Medicine, Medical University of Plovdiv, as well as in outpatient clinics and rheumatology departments. Quantitative analyses of cytokine levels, drug bioavailability, and drug-induced neutralizing antibodies were conducted in specified laboratories under the supervision of qualified professionals.

Statistical analysis

Data analysis involved a rigorous process, including verification, coding, and entry into a computer database. SPSS v. 24 was employed for statistical analyses, encompassing descriptive statistics, parametric and non-parametric tests, linear regression, binary logistic analysis, and ROC analysis. The homogeneity of variations was assessed using the Levene equality test, and correlations in non-normally distributed data were explored using Spearman rank analysis. Multivariate regression analysis was utilized to calculate the relative risk (RR) for disease development. The inclusion of a wide array of clinical and laboratory variables allowed for a comprehensive evaluation of the impact of TNF-α blockers on patients with RA, AS, and PsA.

RESULTS

The process of constructing prognostic models for the emergence of drug-induced neutralizing antibodies in patients with RA, PsA, and AS treated with TNF-α blockers within the analyzed patient group followed these steps:

- Identifying a sample of 213 patients to isolate independent, statistically significant prognostic factors for the emergence of drug-induced neutralizing antibodies in these patients.
- Analyzing all factors proven to be statistically significant in univariate analysis through multivariate analysis, employing a regression model with a stepwise selection procedure.
- Ensuring the proportionality of all covariates included in the regression model.
- Investigating the existence of individual data instances with notably deviating values for the model-influencing covariates.
- Repeating a multifactorial analysis involving all 213 patients.
- Evaluating the goodness-of-fit of the model, which assesses its adequacy in describing the resulting variable.

The significant variables identified through unifactorial regression analysis or correlation analysis were tested to establish a predictive mathematical model for the emergence of drug-induced neutralizing antibodies in patients with RA, PsA, and AS treated with TNF-α blockers. These variables included gender, age, education, excess weight, smoking, alcohol intake, concomitant pathology, dosage regimen of methotrexate below 10 mg per week, disease severity, ESR ≥28 mm, CRP ≥10 mg/L, VAS for pain as assessed by the patient, scales and activity indices such as HAQ-DI, DAS-28 for patients with RA, BASFI, ASDAS, BASDAI for patients with AS, and DAPSA for patients with PsA. Additionally, the levels of TNF-α and IL-6, as determined through ROC analysis, played a role in distinguishing patients from healthy controls, as well as the bioavailability of adalimumab exceeding the specified laboratory threshold value.

The equation used to calculate the risk likelihood estimate is as follows:

Z – linear combination
Z = Vo+B1o1+B2o2+B3o3+... In Hoch
E – Non-zero number – 2.71.
Vo – represents the constant unique to each mathematical model of probabilities
B1o1 – constant of the first indicator
B2o2 – constant of the second indicator, and so forth

High risk of drug-induced neutralizing antibodies in patients with RA, PsA, and AS treated with TNF-α blockers was associated with factors including age over 55 years, BMI over 25, smoking, methotrexate dosage below 10 mg per week, and disease duration exceeding 12 years, as shown in **Table 3**.

Table 3. A prognostic mathematical model for the emergence of drug-induced neutralizing antibodies in patients with RA, PsA, AS treated with TNF-α blockers by demographic and patient history evaluation – multivariate regression analysis

Indicators	Regression coefficient (B±SE)	Relative risk	95% CI for EXP (B)		R
			Lower	Upper	
Age 55+	4.869±1.038	3.0166	1.005	9.383	0.000
BMI over 25.2770	0.802±0.264	2.229	1.328	3.741	0.002
Smoking more than 15 cigarettes a day	4.772±1.037	1.182	1.1820	6.8208	0.000
Use of methotrexate below 7.5 mg/week	1.342±0.321	5.6201	3.541	7.228	0.000
Disease duration over 15 years	1.868±0.229	1.154	1.154	1.154	0.000
Constant	−4.519±1.069	0.001			0.000

χ^2 =61.34, K=5, p<0.001

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Our mathematical models are based on patient history information and the medical documentation provided by patients at their initial appointments with the physician. These models encompass a comprehensive range of sequential serological and immunological parameters.

A heightened risk of developing drug-induced neutralizing antibodies in patients with RA, PsA, and AS treated with TNF-α blockers is associated with specific criteria, including:

- Elevated ESR ≥28 mm
- Elevated CRP ≥10 mg/L
- Significantly different levels of TNF-α and IL-6 compared to the control group of individuals corresponding to the respective disease
- Evaluation of adalimumab drug bioavailability conducted prior to treatment initiation **(Table 4)**.

These criteria aid in identifying patients with a higher risk of developing drug-induced neutralizing antibodies.

A simplified predictive mathematical model, information on disease limitation, morning stiffness, and disease activity indexes were obtained in Steps 3 and 4 by multivariate regression analysis **(Table 5)**.

This model is preferable because it only collects information from the patient without the need for clinical laboratory tests.

The following mathematical model was obtained with the serological indicators included, drug bioavailability of adalimumab (model for RA patients only), and activity indices **(Table 6)**.

Table 4. A prognostic mathematical model for the emergence of drug-induced neutralizing antibodies in patients with RA, PsA, AS treated with TNF-α blockers by evaluation of serological and immunological parameters – multivariate regression analysis (RR)

Factors	Regression coefficient (B±SE)	Relative risk	95% CI		*P*
			Lower	Upper	
ESR >48 mm	4.137±0.909	3.627	1.542	7.202	<0.0001
CRP >48 mg/L	4.305±0.797	4.085	3.559	13,520	<0.0001
TNF-α for					
RA=40.8000 pg/ml	2.330±0.947	2.120	2.067	13.781	<0.0001
AS=42.1200 pg/ml	0.394±0.559	1.775	1.994	11.223	<0.0001
PsA=53.500 pg/ml	6.123±1.048	5.762	3.341	13.440	<0.0001
IL-6 ng/ml for					
RA=14.2150 ng/ml	1.378±1.019	3.969	0.542	9.412	<0.0001
AS=13.8600 ng/ml	1.322±0.992	2.004	1.116	4.443	<0.0001
PsA=13.5500 ng/ml	6.455±2.058	5.391	5.922	12.390	<0.0001
Medicinal bioavailability of adalimumab – below 3.3250 ng/ml	2.682±0.758	4.9182	3.312	8.5616	<0.0001

χ^2 =53.29, K=5, p<0.001; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis

Table 5. A prognostic mathematical model for the occurrence of drug-induced neutralizing antibodies in patients with RA, PsA, AS treated with TNF-α blockers by scale evaluation and disease activity indices – multivariate regression analysis (RR)

Factors	Regression coefficient (B±SE)	Relative risk	95% CI for EXP (B)		R
			Lower	Upper	
Morning stiffness over 58 minutes	1.819±0.343	3.164	1.147	6.076	<0.0001
HAQ-DI >2.3239	2.246±0.316	4.453	3.099	7.973	<0.0001
Duration of the disease over 15 years	3.401±0.657	3.526	2.930	9.257	<0.0001
Activity indices					
RA – DAS-28 >6.10	2.633±0.393	3.918	1.9946	10.096	<0.0001
AS – BASDAI >5.1400	3.981±1.221	4.9221	3.772	7.248	<0.0001
PsA – DAPSA >38.0	1.665± 0.779	1.955	1.008	3.883	<0.0001
Constant	−3.221±0.546	0.004			<0.001

χ^2 (chi-square)=34.12, K=4, p<0.001; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis

Table 6. A prognostic mathematical model for the emergence of drug-induced neutralizing antibodies in patients with RA, PsA, AS treated with TNF-α blockers by serological evaluation, drug bioavailability for adalimumab and disease activity indices – multifactorial regression analysis (RR)

Factors	Regression coefficient (B±SE)	Relative risk	95% CI for EXP (B)		R
			Lower	Upper	<0.0001
ESR >48 mm	1.856±0.354	2.397	1.992	5.198	<0.0001
CRP >48 mg/L	2.063±0.328	3.869	2.303	8.135	<0.0001
Drug bioavailability of adalimumab – below 3.3250 ng/ml (PA)	2.303±0.389	5.003	4.665	11.391	<0.0001
VAS – for pain over 70.16 mm	2.302±0.391	3.990	1.646	7.480	<0.001
Activity indices					
RA – DAS-28 >6.10	1.503±0.347	4.494	2.278	8.867	<0.0001
AS – BASDAI >5.14	2.345±0.925	3.0661	1.899	8.072	
PsA – DAPSA >38.09	1.503±0.347	2.774	1.404	5.553	
Constant	−6.243±0.597	0.002			<0.0001

χ^2 =31.44, K=5, p<0.001; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis

DISCUSSION

The pursuit of identifying predictors of a favorable clinical response to TNF-α blockers in patients with inflammatory joint diseases, such as RA, AS, and PsA, has been acknowledged in numerous scientific studies.[5-8] According to Hyrich et al.[5], they found a correlation between higher HAQ scores and reduced therapy efficacy, while the concomitant use of NSAIDs and MTX intake was associated with improved clinical responses in patients with RA. Interestingly, this study also revealed that smokers exhibited a less favorable response to therapy, while factors like patient age, disease duration, and previous DMARD use did not significantly impact therapy effectiveness.[5] However, it is worth noting that despite discussing risk factors, these authors did not consolidate them into predictive mathematical models.

In our research, we have constructed several mathematical models aimed at predicting the development of drug-induced neutralizing antibodies in patients with RA, PsA, and AS undergoing treatment with TNF-α blockers. These models incorporate a wide array of demographic, serological, immunological, and disease activity index data. It is important to recognize that in practical clinical settings, physicians may not always be able to assess cytokine levels, drug bioavailability, or antibodies to the medication used. Furthermore, we did not include sex as a predictive element in our models, as our studies indicated that sex does not hold predictive value. Interestingly, these findings differ from those reported by Arends et al.[9], who suggested that younger age, male sex, higher ASDAS values, lower ESR and CRP values, and elevated PtGADA values hold prognostic value for the effectiveness of TNF-α blocker treatment.

In our evaluation of the prognostic value of serum TNF-α and IL-6 levels, we sought to create specific predictive models for each disease, incorporating only these two cytokines. While the medical literature recommends the study of the Cytokine Activity Index, which includes an array of cytokines, such as TNF-α, IL-1, IL-6, GM-CSF, IL-4, IL-5, IL-13, and others[10,11], practical considerations led us to propose predictive mathematical models that focus on the two cytokines most relevant to our study.

Our analysis considered both groups of patients, those with and without serum-neutralizing antibodies treated with TNF-α blockers, as a unified cohort. This approach was adopted because, despite variances in the etiology of RA, AS, and PsA, the ultimate outcome of treatment, as indirectly measured by the presence of neutralizing antibodies, exhibited no substantial difference at 12 and 24 months from the initiation of therapy. These findings diverge from those of Maneiro et al.[12], who suggested that factors like younger age, male sex, high baseline BASDAI, low baseline ESR, low baseline CRP, and HLA-B27 positivity are predictive of a better response to TNF-antagonist treatment in AS patients but not in those with PsA.

Each of the prognostic mathematical models that integrated pharmacovigilance data related to adalimumab's bioavailability yielded highly significant results. This underscores the findings of Jani et al.[13,14], who reported that adalimumab's bioavailability is the most reliable predictor of changes in DAS-28 at the 12-month mark in RA patients monitored over a year. They found a strong regression coefficient of 0.060 (95% CI 0.015, 0.10, p=0.009). These authors, like us, concluded that pharmacological assessments of patients receiving TNF-α blockers offer clinical utility, even in the absence of drug-induced antibodies.

Despite the numerous predictive factors identified for response to biological therapies, consensus among research-

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ers is only shared for a select few. Predicting outcomes in severe rheumatic diseases, indicated by a high HAQ score and prior treatment failure, remains a challenging endeavor, as a high baseline DAS-28 predicts a stronger DAS-28 in a follow-up, irrespective of the type of treatment received. Conversely, younger age, smoking cessation, alcohol abstinence, lower body weight, and a negative serological status prove to be reliable predictors of TNF-α blocker treatment efficacy.

CONCLUSION

The pursuit of clinical and biological markers with predictive value for therapeutic responses in individual patients remains a formidable task. The complexity arises from the fact that treatment responses depend on at least three distinct parameters: the disease's state, drug bioavailability, and the pathophysiological changes occurring in the affected organism. Moreover, each of these parameters is influenced by a myriad of other factors.

Ethics Committee Approval

This study was approved by the Ethics Committee of the Medical University of Plovdiv (approval No. DP- P-8278 /02/13/2018)

Acknowledgements

The authors have no support to report.

Funding

The authors have no funding to report.

Competing Interests

The authors have declared that no competing interests exist.

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Прогностические модели лекарственно-индуцированного образования нейтрализующих антител у больных ревматоидным артритом, псориатическим артритом, анкилозирующим спондилитом, получающих блокаторы TNF-α

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Дата получения: 30 октября 2023 ♦ **Дата приемки:** 23 февраля 2024 ♦ **Дата публикации:** 30 апреля 2024

Образец цитирования: Kraev K, Hristov B, Uchikov P, Kraeva M, Geneva-Popova M, Popova S, Basheva-Kraeva Y, Stoyanova NS, Mitkova-Hristova V. Prognostic models of drug-induced neutralizing antibody formation in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis treated with TNF-α blockers. Folia Med (Plovdiv) 2024;66(2):188-195. doi: 10.3897/folmed.66.e114887.

Резюме

Цель: Целью данного исследования было создание прогностических математических моделей с использованием многофакторного регрессионного анализа для оценки риска развития лекарственно-индуцированных нейтрализующих антител у пациентов с ревматоидным артритом, псориатическим артритом и анкилозирующим спондилитом, получавших альфа-блокаторы фактора некроза опухоли.

Материалы и методы: В течение четырёх лет мы включили в исследование 213 пациентов и разделили их на три группы: группу ревматоидного артрита (n=121), группу болезни Бехтерева (n=50) и группу псориатического артрита (n=42). В исследование была включена также контрольная группа из здоровых людей, состоящая из 31 здорового человека, соответствующих группам пациентов по возрасту, полу, индексу массы тела и состояниям, типичным для больных ревматологией. Прогностические математические модели, основанные на статистически значимых факторах, определённых с помощью одномерного корреляционного и регрессионного анализа, включали историю болезни пациента, а также серологические и иммунологические данные.

Результаты: В исследование были включены все 213 пациентов и 31 здоровый человек из контрольной группы. Анализ данных проводился через 12 и 24 месяца после начала лечения. Во время этого наблюдения у пациентов наблюдался самый высокий процент антилекарственных антител. Через 6 месяцев у 6.57 % пациентов были подтверждены нейтрализующие антитела, которые увеличились до 12.69 % через 12 месяцев и 17.72 % через 24 месяца. Многофакторный логистический регрессионный анализ показал, что наибольшую прогностическую ценность имели такие факторы, как возраст старше 55 лет, избыточный вес, курение и отсутствие лечения метотрексатом в дозе менее 7.5 mg в неделю.

Заключение: Исследование клинических и биологических маркеров, имеющих прогностическую ценность для терапевтического ответа отдельных пациентов, является сложной задачей. Эта сложность возникает из-за взаимодействия по крайней мере трёх различных параметров: состояния заболевания пациента, биодоступности лекарства и патофизиологических изменений в организме пациента, каждый из которых находится под влиянием различных факторов.

Ключевые слова

антилекарственные антитела, прогностическая модель

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