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TREATMENT RESPONSE PREDICTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

Review

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Relevance. A variety of targeted therapies for rheumatoid arthritis (RA) treatment exist. Therefore, reliable predictors are needed that could be used to accurately predict the efficacy or inefficacy of these therapies in individual patients. This could allow clinicians to improve diagnosis and prognosis, to make the treatment personalized and to reduce healthcare expenses.

Objectives: to analyze and systemize the predictors of response to treatment in patients with RA.

Materials and Methods. We analyzed the recently discovered predictors of treatment response in RA patients using papers cited on PubMed, Lilacs, and EMBASE databases from Jan 2005 until Jan 2020. Predictive factors were grouped into four categories: methotrexate (MTX)-treated RA, tumor necrosis factor (TNF)- α inhibitors-treated RA, interleukin (IL)-6 inhibitors-treated RA, and rituximab (RTX)-treated RA.

Results. Based on the results of several studies, predictors of response to methotrexate were high Disease Activity Score (DAS), concentration of myeloid-related proteins 8/14, high P-glycoprotein levels, low serum calprotectin and leptin levels, baseline serum concentration of tumor necrosis factor (TNF)- α , TNF receptor I, interleukin (IL)-1 β , soluble CD163, numbers of CD14+highCD16, vascular cell adhesion molecule, lower expression of hsa-miR-132-3p, hsa-miR-146a-5p, and hsa-miR-155-5p. A positive response to biological therapy was determined by male gender, younger age, lower health assessment questionnaire, erythrocyte sedimentation rate or C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, tender joint count (or swollen joint count) scores, absence of comorbidities, baseline albumin, IL-34, IL-1 β , D-dimer, fibrinogen, matrix metalloproteinase 3, DAS 28 and Simplified Disease Activity Index (SDAI). The plasma interferon (IFN) activity and the IFN beta/alpha ratio, IL-1Ra level were predictive in TNF antagonist-treated patients. Predictors of response to IL-6 inhibitors were anti-citrullinated protein antibody (ACPA)+, baseline Sharp/van der Heijde score, myeloid soluble intercellular adhesion molecule 1, serum levels of sIL-6R, IL-8, calprotectin, and lymphoid activation and bone remodeling markers. The prediction of the best response for rituximab was determined to be a combination of IL-33, rheumatoid factor or ACPA, IgG, and also lower number of previous biological therapies. Genetic factors, such as single-nucleotide polymorphisms at gene locus rs10919563, rs11541076, rs12083537, rs11265618, and rs1801274, and rs396991 can also be used to predict a response to treatment.

Conclusions. One of the leading problems in the development of predictors remains the collection of high-quality and complete information from a large number of patients. For this, it is necessary to develop a digital program for collecting specific data (depending on the specific disease) and developing new algorithms for predicting the response to treatment.

Key words: rheumatoid arthritis, treatment, response, prediction.

Relevance. Many targeted therapies are available for rheumatoid arthritis (RA) treatment. Because of this wide choice of treatment, the management of RA has entered the era of “personalized medicine,” and therefore reliable biomarkers are needed that could be used to accurately predict the efficacy or inefficacy of these therapies in individual patients, thereby improving medical decision-making [7]. Identifying the responsive subpopulation before a therapy is started could allow clinicians to improve diagnosis and prognosis, make treatments personalized and reduce healthcare expenses [48].

Objectives: to analyze and systemize the predictors of response to treatment in patients with RA.

MATERIALS AND METHODS

We analyzed the recently discovered predictors of treatment response in patients with RA using PubMed, Lilacs, and EMBASE databases from Jan 2005 until

Jan 2020. The search terms were rheumatoid arthritis, treatment, response, prediction. Predictive factors were grouped into four categories: methotrexate (MTX)-treated RA, tumor necrosis factor (TNF)- α inhibitors-treated RA, interleukin (IL)-6 inhibitors-treated RA, and rituximab (RTX)-treated RA.

RESULTS AND DISCUSSION

MTX-treated RA

To date, MTX remains the most widely used first drug for treating RA. Due to the long period of use, a lot of information has been accumulated about the prediction of the treatment response.

The simplest to use in practice are predictors based on the use of standard disease activity scores (DAS) and standard laboratory parameters: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). The study conducted by A.Kavanaugh et al (post

hoc analysis of data from the randomized, double-blind OPTIMA and PREMIER studies) revealed that higher time-averaged DAS28 (CRP) was the strongest positive predictor of insufficient response to MTX and clinically relevant radiographic progression at 6 months ($p < 0.001$ for both). Additionally, high values of time-averaged DAS28 (CRP) were also positive predictors of insufficient MTX response and clinically relevant radiographic progression. [53]. David L. Scott provided a systematic review of calprotectin as a biomarker. This biomarker is also often used in routine practice. When addressing the incremental predictive value, baseline calprotectin was the only statistically significant independent determinant of therapy response in full multivariate analysis with adjustments for DAS28 and 68-tender joint counts. Initiation of conventional treatment in patients naive for disease-modifying antirheumatic drugs (DMARDs)/glucocorticoid (GC) resulted in the near normalization of calprotectin levels after 3 months. Levels were unrelated to doses of GC and/or MTX. Changes in serum calprotectin positively correlated with changes in serum CRP ($r = 0.48$, $p = 0.002$), DAS28 ($r = 0.39$, $p = 0.01$), and swollen joint count ($r = 0.54$, $p < 0.001$). Decreasing in calprotectin level was significant in treatment responders using RTX as well as adalimumab (ADA) or infliximab (INF) [1].

The possibility of using various cytokines has also been studied quite a lot. Multiple studies found that serum concentrations of the following cytokines are not correlated with MTX efficacy: IL-1 receptor antagonist, IL-1 β , IL-6, IL-8, IL-10 and IL-12 [59]. Conversely, decreased baseline serum concentration of TNF- α has been reported as predictive of MTX response [35]. However, in another study focusing on early RA patients, serum TNF- α was not predictive of MTX response [3]. Recently, it was found that a higher concentration of myeloid-related proteins (MRP) 8 and 14 in the serum of RA patients before MTX monotherapy is associated with larger therapeutic response to MTX. Thus, serum MRP 8 and 14 are promising biomarkers that could be used to predict MTX response [45]. Interestingly, MRP8/14 was a better predictor of response than CRP and ESR, especially for early arthritis (< 1 -yr duration). Seitz et al found that level of IL-1 β produced by peripheral blood mononuclear cells was associated with ACR50 and ACR70 response in RA patients following 6 months of treatment with MTX [34]. Other cytokine, myeloid progenitor inhibitory factor-1 is a chemokine that is involved in chemoattraction of resting T cells and monocytes. Its lower baseline level predicted a good response to MTX at week 12 in A Sandhu et al study [11].

Alex et al developed a Cytokine Activity Index based on 16 different serum cytokines measured in RA patients starting MTX treatment; their model was found to be associated with treatment response, but has not been validated in a prospective cohort [2].

MTX has been shown to inhibit cytokine production by T cells, so immunological predictors are a logical source

of potential biomarkers of treatment response. Haroon et al found that in vitro suppression of TNF α in DMARD-naïve RA patients using MTX was predictive of clinical response, but these findings have not been replicated in vivo [20]. Greisen et al found that pre-treatment levels of soluble CD163 correlated with CRP levels, possibly serving as a molecular marker of response or resistance to MTX [18].

Sanches Peres et al found reduced expression of CD39+ Tregs in MTX non-responders compared with MTX-responsive patients after 3 months of treatment [46]. In monocytes, Chara et al found that the pre-treatment absolute number of circulating monocytes, and the numbers of CD14+highCD16- and CD14+highCD16+ subset cells were predictive of the clinical response to MTX in treatment-naïve RA patients, with a sensitivity and specificity of $>70\%$ and $>88\%$, respectively. The lack of effect of MTX treatment on monocyte CX3CR1 expression is further supported by the absence of modification of its constitutively increased expression in CD14+lowCD16+ monocytes in non-responders [5].

However, none of these immunological studies have been validated in larger, independent cohorts, so it remains an area of research to identify potential biomarkers of MTX treatment response.

The results of high-quality clinical studies that examine different combinations of markers as possible tools for predicting are promising. Four of the 12 biomarkers in Karen Hambarzumyan et al study (CRP, leptin, TNF-RI, and vascular cell adhesion molecule (VCAM-1)) significantly predicted low disease activity (DAS28 ≤ 3.2). Significantly higher proportions with low disease activity (LDA; DAS28 ≤ 3.2) among patients with lower versus higher levels of CRP or leptin (40% vs 23%, $p = 0.004$, and 40% vs 25%, $p = 0.011$, respectively) were shown, as well as among those with higher versus lower levels of TNF-RI or VCAM-1 (43% vs 27%, $p = 0.004$, and 41% vs 25%, $p = 0.004$, respectively). Combined score based on these biomarkers, adjusted for known predictors (smoking, sex, and age) of low disease activity (LDA), associated with decreased chance of LDA (adjusted OR 0.45, 95% CI 0.32–0.62).

Erythrocyte folate levels have also been investigated to determine MTX responsiveness. In one study, a low baseline folate level was associated with a poor response to MTX [10], and low levels of polyglutamated folate were associated with LDA in other study [4].

P-glycoprotein (P-gp) encoded by the multidrug resistance-1 human gene responsible for cross-resistance of mammalian cells to a number of chemotherapeutic agents [37]. RA patients with DMARDs failure had higher serum P-gp levels than patients with a therapeutic response. High P-gp levels increased the risk of DMARD failure (OR 3.36, 95% CI 1.54–7.27, $p = 0.001$). After adjusting for confounding variables, elevated P-gp remained associated with DMARD failure (OR 2.64, 95% CI 1.29–5.40, $p = 0.01$). In recent years, there has

been increasing evidence of the use of micro-RNAs (miRNAs) as possible predictors of response to therapy. Deregulation of some miRNAs has been found in RA [13]. Amita Aggarwal et al study [52] showed that patients who responded to MTX had lower expression of hsa-miR-132-3p, hsa-miR-146a-5p, and hsa-miR-155-5p as compared to non-responders. Receiver operating characteristic curve analysis showed that all three miRNAs were also good predictors of MTX response.

Xia Y et al reported that circulating miR-10a was significantly decreased in RA patients compared to osteoarthritic patients and healthy people. Importantly, circulating miR-10a was up-regulated in RA patients treated with MTX. Moreover, it was identified that circulating miR-10a may serve as a predictor of therapy effectiveness in MTX-treated patients (sensitivity 66.7%, specificity 80%) [23].

In another work, it was shown that the expression of miR-125b in PBMCs of treatment-naïve patients may present a novel biomarker for monitoring the treatment outcome during the early phase of RA. Baseline cellular expression of miR-125b was higher in responders than in non-responders ($p=0.042$) and was a significant and independent predictor of treatment response at 3 months (OR 3.717 95 % CI 1.005 to 13.745; $p=0.049$) [24].

TNF- α inhibitors- treated RA

In current practice, patients who respond inadequately to conventional therapies usually receive TNF- α inhibitors [53]. However, patient heterogeneity hinders identification of predictive biomarkers and accurate modeling of anti-TNF drug responses. It should also be noticed that markers found in one ethnic population or cohort may not be applicable to others [58].

As for MTX, we began with searching for predictors that are used in routine practice. P Durez et al analyzed data from the GO-MORE study. In the study, patients received 50 mg golimumab (GLM) once monthly for 6 months. LDA and remission were associated with male gender, younger age, lower HAQ (health assessment questionnaire), ESR or CRP, tender joint count (TJC) or swollen joint count (SJC), absence of comorbidities [56].

A similar assay was performed for certolizumab PEGol (CZP). Baseline predictors of response were: lower prior number DMARD, low number prior bDMARD; higher CRP, ESR, tender joint count and swollen joint count scores, DAS28 and Simplified Disease Activity Index (SDAI) ($p<0.05$) scores [57].

Even a simple indicator like kinetics of response turned out to be a reliable predictor of a long-term response. Post-hoc Analysis of the RAPID 1 Trial proofs that absence of DAS28 improvement to CZP during the first 12 weeks of therapy was predictive of a low probability of achieving LDA at Year 1 [59]. In Liqi Bi et al etanercept study has been shown, that baseline albumine ≥ 34.9 g/l or ESR ≤ 55.5 mm/h might predict a good response at 1st months, while baseline ESR

≤ 60 mm/h, HAQ ≤ 1.31 , and IL-34 ≤ 194.1 pg/ml might predict a good response at 3rd month [12].

In another retrospective cohort study performed by Han-Na Lee et al, high baseline neutrophil-to-lymphocyte ratio (NLR) (OR 5.57, 95% CI 1.45–26.99, $p=0.014$) and platelet-to-lymphocyte ratio (PLR) (OR 4.24, 95% CI 1.07–16.81, $p=0.04$) were independently associated with a higher risk of non-response at 12 weeks. High baseline NLR was associated with an increased risk of anti-TNF- α agent withdrawal due to lack of efficacy (HR 2.12, 95% CI 1.02–4.44, $p=0.045$) [31].

Mikkel Stergaard et al provided an investigation to compare treatment responses in patients treated with ADA, etanercept, or INF. 2326 RA patients were included from the Danish DANBIO register. Older age, low functional status, and concomitant GC treatment were negative predictors of a clinical response [21].

Another promising biomarker to predict response to bDMARDs is serum concentration of MRP8/14 protein complex. In IY Choi et al study responders had significantly higher MRP8/14 protein complex levels compared with non-responders. Logistic regression analysis showed that having high MRP8/14 baseline levels increased the odds of being a responder by 3.3 up to 55. In contrast, MRP8/14 levels were stable in non-responders [6].

In SC Nair et al study the probability of response increased with higher baseline MRP8/14 complex levels (OR = 1.39) too, but differentially between the TNF-blockers and RTX, and also increased with higher DAS28 at baseline (OR = 1.28). Rheumatoid factor (RF) positivity, higher HAQ, and previous use of a TNF-inhibitor decreased the probability of response [39]. According to authors' conclusion multitoool (calprotectin, DAS 28, HAQ and RF-positivity) may be further developed and used to personalize treatment. Correlation of seropositivity for RA and ACPA with treatment response was also found for T cell blocker, abatacept (ABA). JE Gottenberg et al investigated data from 9 observational RA registries in Europe (ARTIS [Sweden], ATTRA [Czech Republic], BIOBADASER [Spain], DANBIO [Denmark], GISEA [Italy], NOR-DMARD [Norway], ORA [France], Reuma.pt [Portugal], and SCQM-RA [Switzerland]). Even after adjustment for sociodemographic and disease- and treatment-related confounders, RF and ACPA positivity were each associated with a lower risk of ABA discontinuation for any reason, compared to RF-negative and ACPA-negative patients. Similar associations with RF and ACPA were observed for discontinuation of ABA treatment due to ineffectiveness [17].

The plasma IFN activity, the IFN beta/alpha ratio, and the IL-1Ra level were predictive of the therapeutic response in TNF antagonist-treated RA patients, indicating that these parameters might define clinically meaningful subgroups of RA patients with distinct responses to therapeutic agents [37]. In 35 RA patients

on TNF antagonist therapy plasma type I, IFN activity at baseline was significantly associated with clinical response (OR 1.36 [95% confidence interval 1.05-1.76], $p = 0.020$), with high baseline IFN activity associated with a good response. Changes in DAS28 scores were greater among patients with a baseline plasma IFN beta/alpha ratio >0.8 (indicating elevated plasma IFN beta levels). Elevated baseline IL-1Ra levels were associated with better therapeutic outcomes (OR 1.82 [95% CI 1.1-3.29], $p = 0.027$).

N. Ishiguro et al conducted a retrospective observational study using the multicenter registry data in Japan (Tsurumai Biologics Communication registry: TBCR). It has been shown, that effectiveness at week 52 could be predicted using baseline serum matrix metalloproteinase 3 (MMP-3) [22].

Evaluation of genetic factors can also be used to assess the likelihood of a response to treatment. Robert M. Plenge et al. tested 31 RA risk alleles for associations with the response to anti-TNF therapy. Only single-nucleotide polymorphisms (SNPs) at gene locus rs10919563 showed a significant association ($p < 0.01$) with a EULAR good response. The major allele (G allele), which is a known predictor of RA risk, is the same allele that was found to be a predictor of favorable response [8].

Another study looked at the gene combinations identified in eight transcriptome studies done to identify genetic features predicting the response to INF in 374 patients. The response was associated with only five genes (FKBP1A, FGF12, ANO1, LRRC31, and AKR1D1). The 5-gene model showed a good predictive power in random- and prospective-designed studies, with AUC = 0.963 and 1.000, and it was also applicable at the early phase of treatment (at week 2) for predicting the response at week 14 (AUC = 1.000) [25]. Sode et al study validates rs11541076 in IRAK3, negative regulator of TLR signalling, as a predictor of anti-TNF treatment response, and suggests true positive associations of previously reported SNPs within genes encoding activators/inhibitors of NF- κ B [55].

IL-6 inhibitors-treated RA

Recently, several IL-6 inhibitors have become available for clinical use. G Karpouzas et al had investigated sirukumab in 1,670 pts with active RA refractory to DMARDs. ORs showed that patients were significantly more likely to be radiographic non-progressors with sirukumab if they were ACPA+, had a baseline Sharp/van der Heijde (SHS) radiographic damage score $>$ cohort median SHS, or had a baseline SHS >7) [27]. According to sirukumab SIRROUND-T and -D studies worsening in CDAI at Week 4 was predictive of non-response at Week 16 [9]. Thus, it is possible to improve the assessment of the need to switch to another drug within a month after starting.

Cem Gabay et al had demonstrated that myeloid soluble intercellular adhesion molecule 1 (sICAM-1)

was predictive of DAS(CRP) and LDA response in the sarilumab at week 12 in contrast to MMP-3, collagen type I MMP-cleaved fragment, collagen type III MMP-cleaved fragment C3M, IL-8 and calprotectin, and lymphoid activation (chemokine, CXC motif, ligand 13 (CXCL13), CXCL10, B cell-activating factor), and bone remodeling (receptor activator of nuclear factor- κ B (NF- κ B) ligand, osteoprotegerin and osteocalcin) [15].

The largest amount of data regarding the prognosis of response in this group of drugs was accumulated for tocilizumab (TCZ), which was approved earlier [42].

Toshihisa Kojima et al in their retrospective study have found that higher CRP levels at baseline was a significant and independent factor in predicting normal CRP levels over 52 weeks (HR 0.86 per 1 mg/dL). In contrast, disease duration, concomitant MTX use and previous TNF inhibitor failure were not significant factors. Patients with normal CRP levels at 12 weeks of TCZ treatment achieved better clinical outcomes, including remission based on DAS28-ESR criteria, compared to patients with elevated CRP levels at 12 weeks [31].

Tatsuya Koike et al aimed to identify factors that could predict the effects of TCZ therapy in patients with RA in the early period after starting TCZ treatment. Serum levels of IL-1 β , D-dimer and fibrinogen were measured before and after 4 weeks of TCZ therapy. Low D-dimer and IL-1 β levels at week 4 predicted greater decrease in disease activity after 52 weeks of treatment ($p = 0.005$ and $p < 0.001$, respectively). These markers might be more useful than current inflammatory markers for early-stage prediction of response to TCZ in RA [43].

Lennart T. H. Jacobsson et al searched for predictors of drug termination. Patients were identified in the Swedish Rheumatology Quality (SRQ) register. Logistic regression analyses showed that significant predictors for EULAR good response vs no response were low HAQ level, high DAS28 score and not being treated with GC at baseline. Age, disease duration, having seropositive RA, initial level of CRP or ESR, concomitant treatment with any DMARD and previous exposure to biologics were not significant predictors of EULAR good response [14].

As for another bDMARDs, seropositivity in RF and anti-CCP play a role on prediction of TCZ treatment response. Because IL-6 induces B-cell differentiation and is thought to lead to the formation of IgM-RF and anti-CCP antibodies, TCZ might act well in patients with RA with high titers of autoantibodies. Although Kawashiri SY et al [28] found that the rate of high titer IgM-RF patients was dominantly distributed in the remission group toward TNF inhibitor-naïve patients, logistic regression analysis identified that not previous anti-TNF therapy but IgM-RF was an independent predictor of CDAI remission in patients treated with TCZ, suggesting that the influence of IgM-RF in regard to CDAI remission was superior to the influence of previous anti-TNF therapy.

It is tempting to speculate that baseline serum levels of sIL-6R, rather than those of IL-6, are associated

with clinical response to TCZ. To test this hypothesis, Takeuchi T. et al analyzed serum levels of IL-6 and sIL-6R before TCZ treatment and evaluated their association with clinical remission. Multivariate analysis confirmed us that sIL-6R was solely a significant predictor. A cut-off sIL-6R level of 72.6 ng/mL discriminated between SDAI remission and non-remission with a sensitivity of 67% and a specificity of 72%, CDAI remission with 65% and 69%, and DAS28-ESR remission with 59% and 81%, respectively [41].

Not only IL-6 serum levels have an impact on TCZ treatment response. In the study conducted by M Maldonado-Montoro et al, it was confirmed that RA patients treated with TCZ showed better EULAR response, remission, LDA and DAS28 improvement rates when a lower number of bDMARDs were previously administered. The AA genotype for rs12083537 and CC for rs11265618 polymorphisms may act as predictors of good response LDA [36].

In another retrospective prospective cohort study dedicated to gene polymorphism it was also shown, that patients carrying the FCGR3A rs396991-TT genotype treated with TCZ showed higher EULAR R response (OR, 5.075; 95%CI, 1.20–21.33; $p = .027$) at 12 months. In comparison, those who were naive for bDMARDs at the beginning of treatment showed satisfactory EULAR response, higher remission, and greater improvement in DAS28 at 6 months. Younger age at start of TCZ treatment was associated with satisfactory EULAR response at 18 months and greater remission at 6 and 18 months. Subcutaneous TCZ administration was associated with higher remission at 6 months and improved low disease activity rate at 12 months [26].

Several studies indicate that DNA microarray is a powerful tool that can be used to identify genes that may be biomarkers for the prediction of clinical responses to TCZ. In a prospective multicenter study by Hiroshi Nakajima et al, dedicated to Biomarkers Identified by Analysis of Gene Expression, a Genome-Wide DNA Microarray was used. Of 19,416 genes examined, 4 genes were identified as predictive biomarkers of moderate-to-good responses, ROC analysis showed that the AUC was 0.693 for IFI6, 0.920 for MT1G, 0.813 for MX2, and 0.627 for OASL [49]. Among the 4 genes identified in this study, IFI6, MX2, and OASL were type I IFN response genes. This data, such as previous reports, suggest that both IL-6 and TNF α blocking therapies for RA are more likely to be efficacious when IFN activity is increased. The fourth one, MT1G encodes metallothionein-1G, a member of the metallothionein (MT) proteins. MT proteins have also been reported to be involved in immune and inflammatory responses.

All these studies need to be confirmed in independent cohorts. In all previous studies TCZ was the first line biologic therapy, but in a cohort observational multicenter study (Narváez J et al) 126 RA patients were treated with TCZ as a first- or second-line biological therapy. The

predictive factors increasing the likelihood of clinical remission at 3 months were baseline ESR > 30 mm/h (OR: 19.07, 95% CI: 2.720–133.716), baseline CRP > 10 mg/L (OR: 4.95; 95% CI: 1.464–13.826), and the presence of extra-articular manifestations of the disease (OR: 15.45, 95% CI: 2.334–102.319). In contrast the factors that decreased it were higher concentrations of hemoglobin (OR: 0.53, 95% CI: 0.319–0.910), higher baseline DAS28-ESR (OR: 0.30, 95% CI: 0.145–0.635), the number of previous DMARDs (OR: 0.41, 95% CI: 0.221–0.779), and biological therapies used (OR: 0.33, 95% CI: 0.155–0.734) [40].

In contrast to above-mentioned, results from Pers YM et al showed, that they did not observe any correlation with disease duration, smoking, gender, RF or ACPA positivity, combination with MTX or another DMARD and failure of previous biotherapy. In multivariate analysis, only young age (<55 years), high baseline CRP >10 mg/l and no history of CVD were associated with a EULAR response [47].

RTX-treated RA

Despite the efficacy of RTX, 30% of treated patients achieve no clinical benefit. In this era of personalized medicine, in which more data on the individual efficacy of these biologic agents is needed, knowledge of the predictors of response to RTX may be crucial for identifying RA patients in whom RTX therapy may not be efficacious. The transcriptomic profile was assessed in J Sellam et al study [50]. From 190 genes the signature for response featured up-regulation of inflammatory genes centered on NF- κ B, including IL-33 and STAT5A, and down-regulation of the IFN pathway. At week 24 post-RTX therapy, genes involved in the development and functions of B cells were the genes most strongly down regulated. All genes related to B-cell development and the B-cell immune response was strongly down-regulated between baseline and week 24, with no difference between responders and non-responders.

In the multi-cohort study conducted by Xavier Mariet it was shown that detectable serum IL-33 (OR 2.40, 95% CI 1.01–5.72; $p=0.047$) was associated with EULAR response at 24 week. Combining IL-33, RF or ACPA, and IgG predicted the response with an OR of 29.61 (95%CI: 1.30–674.79; $p = 0.034$) [51].

Other study in 142 RA patients showed better response in patients with the FCGR2A rs1801274-TT genotype, the FCGR3A rs396991-G allele, and lower number of previous biological therapies [26].

Complex interactions between a multitude of environmental and genetic factors affect disease development and progression in patients with RA. Different types of big data analysis could be used for predictors detection. And the results of the first uses in rheumatology are encouraging. Gaussian process regression model for predicting anti-TNF drug responses in Y Guan study [19] predicts changes in disease activity

scores with a correlation coefficient of 0.406 and shows to be promising in guiding drug selections in clinical practice based on primarily clinical profiles with additional genetic information. Current risk-prediction models for disease development and outcome based on population-wide databases work well on average, but in terms of precision medicine many of the diagnostic and management needs of patients with rheumatic diseases are still unmet [16].

Machine learning (ML) approaches, however, consider all possible interactions between variables according to multi-dimensional non-linear patterns, irrespective of the degree of complexity, while aggressively seeking to capture as many informative and interesting features as possible [30]. In one study [44] ML integration and analysis of histologic and transcriptional data sets identified 3 distinct molecular subtypes of RA that correlated with specific clinical phenotypes. Histologic scores were found to be associated with parameters of systemic inflammation, including the erythrocyte sedimentation rate, CRP level, and autoantibody levels. The low inflammatory subgroup is characterized by high neuronal and glycoprotein gene expression, as well as pain severity scores that are dissociated from the elevated levels of systemic inflammation markers. Another study [33] demonstrates a clinical prediction model for RA mortality using the machine learning method Random Survival Forests that helps to identify five mortality risk groups.

The literature review had some limitations. When searching for sources, the names of individual drugs were not used, but only the word “treatment” as a whole. Only articles in English were analyzed, which could affect the number of sources included. To decrease the impact of these limitations we scrutinized the reference lists of the included studies to identify additional references.

CONCLUSION

Thus, we plan to use ML algorithms to search for new associations between the initial data and the treatment results of patients with RA. To achieve this goal, our Department of Internal Medicine #3 of Bogomolets National Medical University in 2019 is collaborating with the German digital health company Midaia, which provides therapy support for rheumatic disease patients and caregivers. Using an intelligent chat service, the Midaia Application improves patient care and collects health data to develop new algorithms predicting the response to treatment. Our novel approach will integrate disease-specific software and the predictive power of big data analysis and can be able to generate real value for patients, doctors and the healthcare system.

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ПРОГНОЗУВАННЯ ВІДПОВІДІ ЛІКУВАННЯ У ХВОРИХ НА РЕВМАТОЇДНИЙ АРТРИТ. Огляд

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Актуальність. Сьогодні доступна велика кількість різноспрямованої таргетної терапії ревматоїдного артриту (РА), тому існує потреба в надійних предикторах, які могли б бути використані для точного прогнозування ефективності або неефективності окремих препаратів у конкретних пацієнтів. Використання предикторів може поліпшити діагностику та прогнозування, персоналізувати лікування та зменшити витрати на охорону здоров'я.

Мета: проаналізувати та систематизувати вивчені предиктори відповіді на лікування у хворих на РА.

Матеріали та методи. Ми систематизували нещодавно виявлені предиктори відповіді на лікування хворих з РА проаналізувавши тематичні статті цитовані в PubMed, Lilaes та EMBASE з січня 2005 року до січня 2020 року.

Результати. За результатами досліджень, предикторами відповіді на метотрексат виявились високі значення середнього DAS28 (Disease Activity Score), концентрація мієлоїдних білків 8/14, високий рівень P-гр, низькі рівні кальпротектину та лептину, концентрація фактора некрозу пухлини (ФНП)- α в сироватці крові до початку лікування, рецептори ФНП I, інтерлейкіну (ІЛ)-1 β , розчинна форма CD163, кількість CD14+highCD16, молекула адгезії судинних клітин, нижча експресія hsa-miR-132-3р, hsa-miR-146a-5р та hsa-miR-155-5р. Перспективними предикторами відповіді на біологічну терапію у активних хворих на РА є чоловіча стать, молодший вік, нижчий показник HAQ (health assessment questionnaire), швидкість осідання еритроцитів або С-реактивний білок, співвідношення нейтрофілів до лімфоцитів та тромбоцитів до лімфоцитів, кількість болючих або набряклих суглобів, відсутність супутніх захворювань, вихідний рівень альбуміну та інтерлейкіну ІЛ-34, ІЛ-1 β , D-димеру, фібриногену, матричної металопротеїнази 3, DAS 28 и SDAI (Simplified Disease Activity Index). Активність інтерферону (ІФН) у плазмі крові, співвідношення бета / альфа ІФН та рівень ІЛ-1Ra прогнозували відповідь у пацієнтів з РА, які отримували антагоністи ФНП- α . Предикторами відповіді на інгібітори ІЛ-6 були позитивні антитіла до циклічного цитрулінового пептиду (АЦЦП), вихідний показник за шкалою Шарпа / Ван-дер-Хейдена, мієлоїдна розчинна молекула міжклітинної адгезії 1, сироваткові рівні rIL-6R, ІЛ-8, кальпротектину, маркери лімфоїдної активації і ремоделювання кістки. Прогноз кращої відповіді на ритуксимаб, визначався як комбінація ІЛ-33, ревматоїдного фактора або АЦЦП, IgG, а також меншої кількості попередньої біологічної терапії. Генетичні чинники, такі як однонуклеотидний поліморфізм в локусі генів rs10919563, rs11541076, rs12083537, rs11265618 і rs1801274 і rs396991, також можуть бути використані для прогнозування відповіді на лікування.

Висновки. Однією з провідних проблем розробки предикторів залишається збір якісної та повної інформації серед великої кількості пацієнтів. Для цього необхідно розробити цифрову програму для збору специфічних даних (в залежності від конкретного захворювання) і створення нових алгоритмів для прогнозування відповіді на лікування.

ревматоїдний артрит, лікування, відповідь на лікування, прогнозування.

ПРОГНОЗИРОВАНИЕ ОТВЕТА НА ЛЕЧЕНИЕ У ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ. Обзор

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Актуальность. Сегодня доступно большое количество разнонаправленной таргетной терапии ревматоидного артрита (РА), поэтому существует необходимость в надежных предикторах, которые могли бы быть использованы для точного прогнозирования эффективности или неэффективности отдельных препаратов у конкретных пациентов. Использование предикторов может улучшить диагностику и прогнозирование, персонализировать лечение и уменьшить расходы на здравоохранение.

Цель: проанализировать и систематизировать изученные предикторы ответа на лечение у больных РА.

Материалы и методы. Мы систематизировали недавно определенные предикторы ответа на лечение пациентов с РА, проанализировав тематические статьи, цитируемые в PubMed, Lilacs и EMBASE с января 2005 года по январь 2020 года.

Результаты. На основе результатов ряда исследований, предикторами ответа на метотрексат оказались высокие значения по шкале DAS28 (Disease Activity Score), концентрация миелоидных белков 8/14, высокий уровень Р-гр, низкие уровни сывороточного кальпротектина и лептина, концентрация фактора некроза опухоли (ФНО)- α в сыворотке крови до начала лечения, рецепторы ФНО I, ИЛ-1 β , растворимая форма CD163, количество CD14+highCD16, молекула адгезии сосудистых клеток, более низкая экспрессия hsa-miR-132-3р, hsa-miR-146a-5р и hsa-miR-155-5р. Перспективными предикторами ответа на биологическую терапию у активных больных РА является мужской пол, молодой возраст, низкий показатель HAQ (health assessment questionnaire), скорость оседания эритроцитов или С-реактивный белок, соотношение нейтрофилов к лимфоцитам и тромбоцитам к лимфоцитам, количество болезненных или припухших суставов, отсутствие сопутствующих заболеваний, исходный уровень альбумина и интерлейкина (ИЛ)-34, ИЛ-1 β , D-димера, фибриногена, матриксной металлопротеиназы 3, DAS 28 и SDAI (Simplified Disease Activity Index). Активность интерферона (ИФН) в плазме крови, соотношение бета / альфа ИФН и уровень ИЛ-1Ra прогнозировали ответ у пациентов с РА, получавших антагонисты ФНО- α . Предикторами ответа на ингибиторы ИЛ-6 были положительные антитела к циклическому цитруллинсодержащему пептиду (АЦЦП), исходный показатель по шкале Шарпа / Ван-дер-Хейде, миелоидная растворимая молекула межклеточной адгезии 1, сывороточные уровни рИЛ-6R, ИЛ-8, кальпротектин, маркеры лимфоидной активации и ремоделирования кости. Прогноз лучшего ответа на ритуксимаб определялся как комбинация ИЛ-33, ревматоидного фактора или АЦЦП, IgG, а также меньшего числа предшествующей биологической терапии. Генетические факторы, такие как однонуклеотидные полиморфизмы в локусе генов rs10919563, rs11541076, rs12083537, rs11265618 и rs1801274 и rs396991, также могут быть использованы для прогнозирования ответа на лечение.

Выводы. Ведущей проблемой разработки предикторов остаётся сбор качественной и полной информации от большого количества пациентов. Для этого необходимо разработать цифровую программу для сбора специфических данных (в зависимости от конкретного заболевания) и создания новых алгоритмов для прогнозирования ответа на лечение.

Ключевые слова: ревматоидный артрит, лечение, ответ на лечение, прогноз.