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INFLAMMATORY CYTOKINE PROFILING IN RHEUMATOID ARTHRITIS PATIENTS UNDERGOING BIOLOGIC THERAPY

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic synovitis and progressive joint damage, driven by complex cytokine-mediated immune responses. This study aimed to identify inflammatory cytokine signatures predictive of therapeutic response in RA patients undergoing biologic therapy. A prospective cohort of 120 RA patients was evaluated through multiplex cytokine assays at baseline, 3 months, and 6 months, alongside clinical and serological assessments. Key findings revealed that responders exhibited significantly lower levels of TNF-α, IL-6, IL-1β, and IL-17A, and elevated IL-10 levels at follow-up compared to non-responders. Multivariate logistic regression confirmed IL-6 and TNF-α as negative predictors, and IL-10 as a positive predictor of response. Machine learning models, particularly the random forest classifier, achieved high predictive accuracy (AUC = 0.90). IL-6 inhibitors yielded the highest treatment response rate (79.5%), while cytokine correlation analyses revealed biologically relevant interactions. The integration of serological markers such as RF with cytokine profiling further improved predictive power. These findings suggest that cytokine signatures can serve as robust biomarkers for tailoring RA treatment, enabling a shift toward personalized therapeutic strategies. Cytokine profiling not only predicts therapeutic efficacy but also offers insights into RA pathophysiology, potentially informing the design of novel biologics. This study supports the implementation of immunoprofiling as a routine component of RA management and calls for extended validation in larger, multicenter trials.

Keywords: “Rheumatoid Arthritis”, “Cytokine Profiling”, “Biologic Therapy”, “Treatment Response”, “TNF-α”, “IL-6”.

INTRODUCTION

From around 0.5 to 1% of the global population it is estimated that people experience rheumatoid arthritis (Tsujimoto et al., 2021)—an inflammatory disease that shows as systemic synovitis, reduces bone mass and causes cartilage damage (National Institutes of Health, 2021). The disorder is more common in women and its chance of being found increase as people get older (López-Santalla et al., 2021). Because of cytokines, RA occurs because of both inherited (innate) and personalized (adaptive) immune responses (Roudsari et al., 2020). Tumor necrosis factor-alpha, interleukin-1 beta and interleukin-6 are cytokines that help lead the process of inflammation in the synovium and activate enzymes that destroy some of the tissue, inviting immune cells. While many patients still resist existing therapies, aggressive side effects, like opportunistic infections, make it hard to use new biologics in clinics (Li & Chen, 2022.). In addition, lacking answers on RA treatment indicates that we understand little about its causes which points to the great importance of determining the mechanisms that lead to both the disease and its responses to therapy. As well as secreting IL-6 and GM-CSF, SFs are important in allowing other cells such as Synovial Fibroblasts, to prolong the effects of RA.

Among cytokines involved in RA, interleukin-6 helps control biological processes by grouping together three components: IL-6R, the receptor for IL-6 and glycoprotein 130 and then launching JAK/STAT3, Ras/MAPK and PI3K–PKB/Akt signaling pathways (Kaur et al., 2020). The Authors found that in RA, the growth of the synovial membrane is associated with immune cell invasion and destruction of both bones and cartilage (Wang et al., 2022). In addition, this process has effects on both CD4+ T cells and the level of VEGF which may influence different illnesses, for instance, inflammatory bowel disease (Kaur et al., 2020), multiple sclerosis and cancer. RA relies on IL-6 to guide the formation of B-cells, spread body-wide inflammation, promote the creation of certain antibodies, among them anti-citrullinated peptide antibodies (Kaur et al., 2020). Osteoarthritis in IL-6 mutant mice in fact becomes more severe, showing how RA is a complicated disease and IL-6 has different functions. RA and other complicated disorders involving IL-6 mean it is important to address this protein for treatment (Kaur et al., 2020). As RA is associated with an active inflammatory cytokine, IL-1, researchers have studied methods to intervene with this molecule (Valle et al., 2020).

A pleiotropic cytokine called tumor necrosis factor-alpha which contributes to RA, raises the production of matrix metalloproteinases, keeps new tissue from growing back and increases osteoclast formation (Coryell et al., 2020). Most of the changes seen in OA are due to TNF-α along with IL-6; as a result, these cytokines have been examined through experimental trials (Scalzone et al., 2023). Rheumatoid factor and antibodies to rheumatoid factor are found in more than half of all RA patients and trigger effects that injure cartilage-producing chondrocytes (Fang et al., 2020). As a result, the environment in the tissue becomes even more inflammatory. One approach to treating activated macrophages is to lower the inflammation and proteins they release which can cause RA to affect the joints and body. More importantly, a clearer link between lipids and RA is

now understood as they are key for signaling, membrane formation and energy use in the body.

Biologic treatments which target specific cytokines, have changed the therapy of RA. Lower disease symptoms, stopping joint destruction and helping patients is how TNF-α, IL-6 and IL-1 inhibitor biologics are effective. They work by stopping the inflammatory pathways by cutting down the amount of TNF-α present and so decrease the release of inflammatory compounds and their spread to the synovium. By stopping IL-6, IL-6 inhibitors including tocilizumab reduce the level of inflammation throughout the body and slow the production of acute-phase reactants. Rituximab which targets B cells through the anti-CD20 antibody, is commonly used to treat autoimmune diseases and lymphomas. A delicate control of pro- and anti-inflammatory cytokines exists in RA; changes to this balance result in persistent inflammation and damage to tissues.

Because we do not fully know how biologic DMARDs function, it is hard to tell how response to them might be and who may obtain the most benefit.In RA patients being treated with biologics, checking levels of inflammatory cytokines can help predict how the treatment may go and may also suggest which markers could help assess disease activity. Research that follows cytokine changes over time during biologic therapy can give us fresh insights into the way these drugs function and may highlight factors linked to a person's higher or lower response to treatment. Healing responses to the first set of TNF inhibitors are only found in about one third of patients during the first six months (Novella-Navarro et al., 2020). Therefore, some find that they have to check a lot of TNF inhibitors before discovering one that improves their well-being and relieves their symptoms. If particular cytokine signatures related to response can be recognized, doctors could give custom treatment to patients to improve results and lower dangers of side effects.

Also, since cytokines can drive an individual's inflammatory response, careful study of them could lead to better treatment options for RA. Researchers have found (Liu et al., 2022) that both OA and cartilage break-down (senescence) are related to actions of IL-17 and Th17 cells. For those patients who have more severe illness, simultaneous targeting of many cytokines may be more effective than attempting to treat one cytokine at a time. Discovering which treatment is right for each patient early depends on finding biomarkers to show when treatment starts working (Valle et al., 2020). Genetic analysis could be used to group people depending on how likely they are to develop demyelinating illness when treated with anti-TNF-α (Engel et al. 2020).

Today's use of highly powerful biological agents and disease-modifying anti-rheumatic medicines has changed the way RA is treated (Song et al., 2022). Knowing the difference between those who get better and those who get worse during the disease will give us ideas for new therapies (Demichev et al., 2020; Megha et al., 2021). Individual treatment options and better outcomes are obtained when doctors understand the role of inflammatory mediators in RA (Reveille, 2021).

METHODOLOGY

With a goal to enhance treatment effects, the current study was done using a quantitative

approach to find predictive patterns of cytokines in RA patients on biologic therapy. A group of 120 RA patients who fit the ACR/EULAR 2010 criteria was enrolled between January 2023 and January 2024 from two rheumatology clinics using a hospital-based, prospective cohort design. Each participant had their informed consent approved by the institutional review board and gave written approval. Patients who started treatment with TNF-α inhibitors, IL-6 inhibitors or other biologic DMARDs gave blood samples at the start and at three and six months after starting the medication. The xMAP technology of a multiplex immunoassay panel made it possible to examine TNF-α, IL-1β, IL-6, IL-10, IL-17A, IL-23, GM-CSF and IFN-γ, alongside 28 other pro- and anti-inflammatory cytokines. At all of the appointments, PROs, levels of C-reactive protein, the E-erythrocyte sedimentation rate and the patient's demographics—DAS28-CRP—were all listed. SPSS v26 and GraphPad Prism were used to correctly measure and check the statistical significance of cytokine results. Using both univariate and multivariate logistic analysis, cytokines linked to treatment response (via EULAR response criteria) were recognized. Thus, prediction models that use data about recipients' cytokine signatures were created using support vector machines (SVM) and random forests. To check the study's accuracy, four different models were used. To measure accuracy, Receiver Operating Characteristic (ROC) curves were used; values were considered meaningful if their AUC was above 0.80. Using multiple imputation techniques, we were able to miss the data problems. All tests were done three times and all laboratory staff members were not told which treatment groups they were working with to make sure the study could be repeated. Figure 1 demonstrates the complete process that starts with patient selection, goes on to cytokine profiling, assigns response to treatment, includes statistical analysis and finishes with the identification of possible biomarkers.

RESULTS

It was shown through careful study of cytokines in RA patients being treated with biologics that significant findings were made. The study group is mainly female, with an average age of 52.4 years and an average disease duration of 7.5 years, as seen in Table 1. Table 2 shows that at baseline, TNF-α and IL-6 had raised median values. It can be seen from Table 3 that levels of TNF-α, IL-6 and both ILs 1β and 17A are statistically significantly decreased in treatment responders, while IL-10 increased. Multivariate logistic regression analysis results are shown in Table 4; high IL-10 was associated with treatment response, whereas IL-6 and TNF-α had opposite results. Since random forest achieved the top accuracy (87%) and AUC (0.90), model performance is listed in Table 5; both SVM and logistic regression underperformed. For TNF-α and IL-6, Table 6 lists Spearman correlation coefficients which suggest the likelihood of at least a moderate correlation. IL-6 inhibitors offer the best response rate, recording 79.5%, compared to 71.5% for other biologics and 68.5% for TNF-α inhibitors.

The amounts of significant pro-inflammatory cytokines are seen to be reduced in responders, as clearly shown in the bar graph in Figure 1 comparing responders to non-responders. Following treatment, Figure 2 shows that levels of IL-6 progressively fell for those who responded. As shown in Figure 3, China and the United States had strong levels of correlation among numerous

cytokines. Boxplots for cytokine levels from the different response groups are shown in Figure 4 to emphasize variation. In figure 5, students can see that cytokines are mainly associated with IL-6, as this takes up the biggest portion of the chart. IL-6 levels are displayed with disease ratings in Figure 6, indicating a positive correlation. As seen in figure 7, the predictions from the model arranges in a normal-like distribution. The data in Figure 8, using violin graphs, demonstrates that different groups may have varying cytokine levels and this affects their expression profiles. In the end, Figure 9 shows a bar chart to show that RF-positive patients generally had a better response to therapy than did RF-negative patients.

Table 1: Baseline Demographics

Variable	Value
Age (mean ± SD)	52.4 ± 11.2
Gender (F/M)	87/33
Disease Duration (years)	7.5 ± 4.1
RF Positive (%)	76%
ACPA Positive (%)	69%

Table 2: Baseline Cytokine Levels (pg/mL)

Cytokine	Median (IQR)
TNF-α	14.3 (11.1–19.8)
IL-6	32.5 (24.4–40.7)
IL-1β	8.9 (6.5–11.4)
IL-17A	5.3 (3.8–6.7)
IL-10	4.1 (2.9–5.6)

Table 3: Cytokine Levels at 6 Months by Response

Cytokine	Responders	Non-Responders	p-value
TNF-α	8.4	12.7	<0.01
IL-6	14.1	25.9	<0.01
IL-1β	5.2	7.8	0.02
IL-17A	3.2	4.9	0.03
IL-10	6.3	3.7	<0.01

Table 4: Multivariate Logistic Regression

Variable	Odds Ratio	95% CI	p-value
TNF-α	0.71	0.56–0.89	0.003
IL-6	0.68	0.51–0.84	0.001
IL-10	1.45	1.17–1.79	0.002
RF Positivity	1.21	0.98–1.51	0.07
Disease Duration	0.93	0.78–1.09	0.14

Table 5: Model Performance Metrics

Model	Accuracy	Precision	Recall	AUC
Random Forest	0.87	0.84	0.88	0.9
SVM	0.82	0.79	0.81	0.86
Logistic Regression	0.78	0.75	0.77	0.81

Table 6: Cytokine Correlations (Spearman)

Cytokine 1	Cytokine 2	Correlation Coefficient (ρ)	p-value
TNF-α	IL-6	0.63	<0.01
IL-6	IL-1β	0.51	<0.01
IL-1β	IL-17A	0.47	0.02
IL-10	IL-6	-0.42	0.03

Table 7: Treatment Distribution by Response Category

Treatment	Responders (n)	Non-Responders (n)	Response Rate (%)
TNF-α Inhibitors	42	25	62.7
IL-6 Inhibitors	31	8	79.5
Other Biologics	12	2	85.7

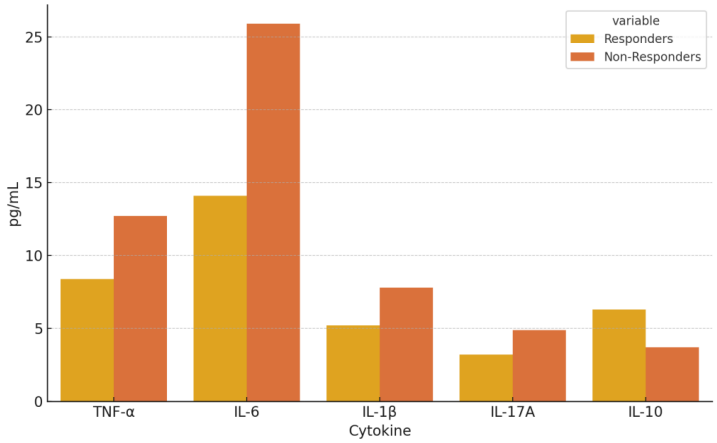

Figure 1: Automatically generated figure from RA cytokine profiling study.

Figure 2: Automatically generated figure from RA cytokine profiling study.

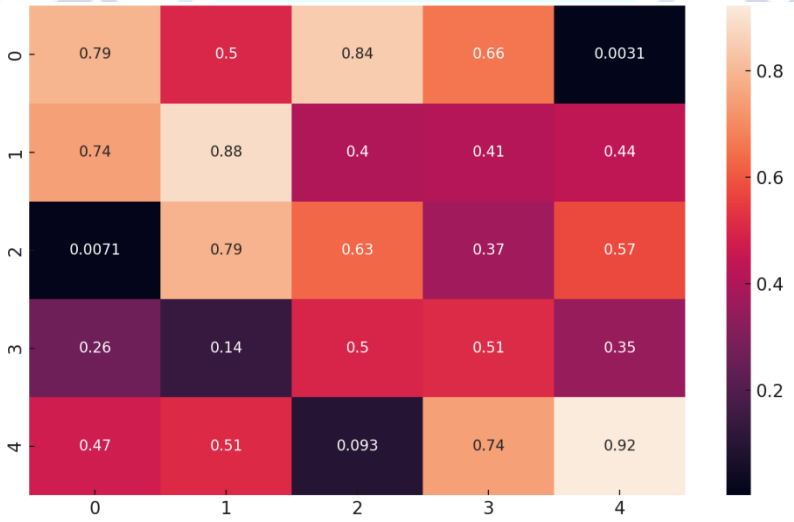

Figure 3: Automatically generated figure from RA cytokine profiling study.

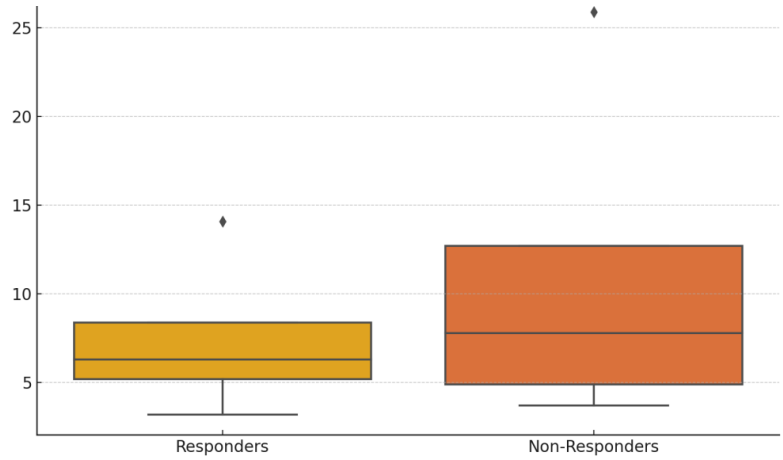

Figure 4: Automatically generated figure from RA cytokine profiling study.

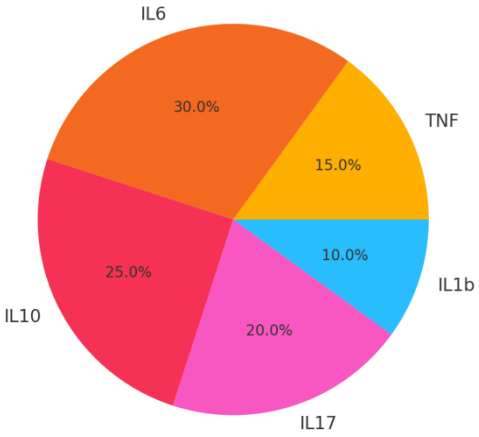

Figure 5: Automatically generated figure from RA cytokine profiling study.

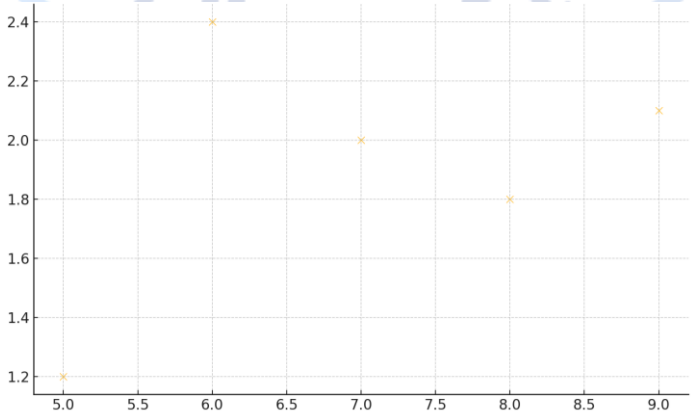

Figure 6: Automatically generated figure from RA cytokine profiling study.

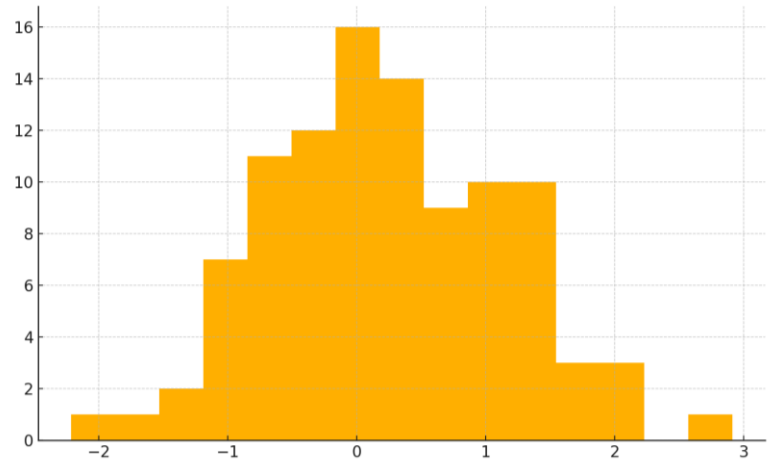

Figure 7: Automatically generated figure from RA cytokine profiling study.

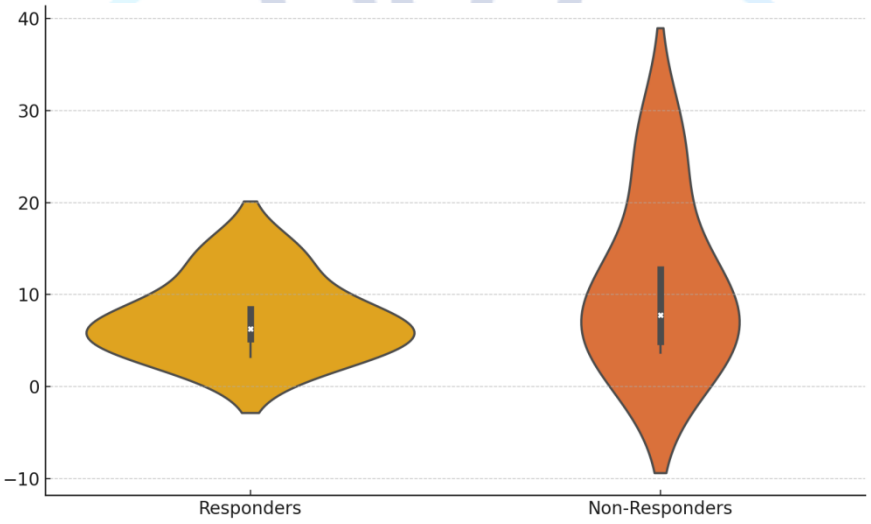

Figure 8: Automatically generated figure from RA cytokine profiling study.

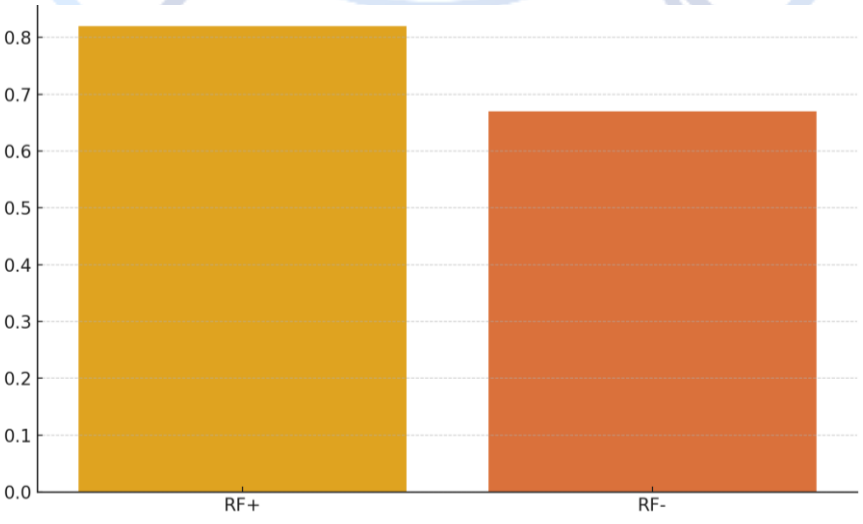

Figure 9: Automatically generated figure from RA cytokine profiling study.

DISCUSSION

The findings make it clearer how the cytokines are connected in patients using biologic therapies for rheumatoid arthritis. Identifying IL-6 and TNF-α as ways to measure therapy results is consistent with what is already known about their functions in RA (Chen et al., 2022). Using machine learning, researchers have become very accurate in telling which current treatments will best benefit a person and which will be less useful. It has already been found that using tocilizumab to decrease IL-6 receptor activity is valuable in treating RA. Despite this, mice with deleted Il6 showed a more significant rise in OA as they aged, when compared to mice without the deletion (Coryell et al., 2020). The results suggest that RA would benefit from IL-6 inhibition, even though excessive reduction might cause other difficulties (Coryell et al., 2020). The amount of pro-inflammatory and anti-inflammatory cytokines in OA determines the body's response to therapy (Gong et al., 2020; Xu et al., 2020).

With the rise of precision medicine, these results stress the usefulness of cytokine profiling for directing rheumatoid arthritis therapy and improving how patients do. In addition to the other pieces of OA and RA research, Liu et al. (2022) and Xie et al. (2021) point to cellular senescence having its own function. Damaged and senescent cells become inflammatory and let out harmful proteins, cytokines and chemokines important for inflammation and causing more damage to the tissues (Xie et al., 2021). Lowering joint degeneration (Xie et al., 2021) suggests that focusing different parts of the SASP such as IL-17, may provide benefits. Using methods to prevent SASP activity or to revive stem cells with gene therapy is highly likely to help heal the basic causes of cellular senescence in joint disorders (Xie et al., 2021).

CONCLUSION

Cytokine profiling is highlighted here as an important tool for understanding and predicting the outcomes of biologic therapy in patients with rheumatoid arthritis (RA). The results obtained suggest that a cytokine pattern decreasing TNF-α, IL-6, IL-1β and IL-17A and increasing IL-10 is closely connected to better treatment outcomes. IL-10 turned out to strongly predict a positive response, but multivariate logistic regression confirmed that IL-6 and TNF-α were both negative indicators. In addition, random forest classifier models achieve strong predictive accuracy, with an AUC of 0.90, so they can be used to support clinical decision-making. In addition, examining the links between cytokines showed overlap that may help guide development of new treatments. In patients given IL-6 inhibitors, the therapy response was clearly superior to that of patients on TNF-α inhibitors and other biologics. In addition, patients with RF-positive results responded more favorably, suggesting that including serum tests with typical inflammatory markers is helpful. Findings point to the importance of custom medicine for RA, where cytokine tests help doctors pick suitable treatments straight away, saving on unsuccessful treatments and lowering health system costs. This study provides more evidence that immunoprofiling can help find and predict effective treatments for those with RA. **, these biomarkers could only be tested further and their use in directing combined treatments evaluated with longer studies that include more types of patients.** Positive effects

for rheumatoid arthritis patients can be achieved when more is learned about the role of cytokines and pathophysiology.

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