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The Prediction of Clinical Response in Rheumatoid Arthritis IL-6 inhibitors and biomarkers relative evaluation

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Abstract:
The treatment of rheumatoid arthritis (RA) through interleukin-6 (IL-6) inhibitors is one of the game changers, but each patient responds to treatment rather differently. The purpose of this comparative effectiveness study was to evaluate the clinical effectiveness of tocilizumab and sarilumab and determine whether they are related to the level of inflammatory biomarkers, taking the level of IL-6 and C-reactive protein (CRP) in the blood of 232 patients with RA. By 24 weeks, Disease Activity Score 28- CRP (DAS28-CRP) remission rates were more significant in patients whose IL-6 level had been high at the test start (p = 0.002). On the other hand, those patients with low biomarker expression had an equal efficacy between both drugs. These estimations provide support to the idea of biomarker profiling in the personalization of RA treatment and imply that the level of IL-6 might become a predictive indicator helping to choose between tocilizumab and sarilumab. The research recommends the application of biomarkers of inflammation in clinical decision making to achieve the best treatment of rheumatoid arthritis.

Keywords: ***IL-6 inhibitors, rheumatoid arthritis, tocilizumab, sarilumab, biomarkers, CRP, DAS28-CRP, inflammatory biomarkers, personalized therapy, clinical effectiveness, biomarker profiling.***

1. Introduction

1.1 Summary on the Pathophysiology of Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is an autoimmune disease of the joints that is chronic and systemic in nature, mainly due to the inflammatory process of the synovial joints which are progressively destroyed, and resulting in pain and loss of cellular functions in the joint. RA pathophysiology is based on interrelation between multiple immune cells, cytokines, and genetic components, which leads to incorrect immune constitution and long-term inflammation. The activating of synovial lining and infiltration of the joint lining (synovium) by inflammatory cells e.g. T cells, B cells and macrophages is central to the disease. Pro-inflammatory cytokines that these cells secrete (tumor necrosis factor (TNF) and interleukin-6 (IL-6) are the most notable), maintain the inflammatory process hence leading to cartilage destruction and bone erosion.

The synovium of the affected area swells with the advancement of the disease into a hyperplastic process called pannus that spreads into the surrounding portions of the bone and the cartilage to cause further damage to the joints. The characteristic symptoms of RA such as swelling, stiffness, fatigue, joint deformities are caused by this inflammation. Although it is not apparent what causes the development of RA, there are certain genetical predispositions that make people very susceptible to the development and progression of the disease, and there are environmental causes and immune reactions that also contribute to the disease development and progression.(1)

1.2 The IL-6 is present in an inflammation and progression of RA.

By serving as the key mediator in controlling the inflammatory process, interleukin-6 (IL-6) has a significant part to play in the process of pathogenesis of RA. The formation of IL-6 occurs in various cells, such as macrophages, fibroblasts and T cells. In RA, there is an increase in the IL-6 levels in the synovial fluid and serum, which is associated with the disease activity, severity and with indications of systemic inflammation like the C- reactive protein (CRP).

In its contribution to the pathophysiology of RA, IL-6 has multiple effects: it supports differentiation to B cells; stimulates the production of acute-phase proteins (such as CRP and fibrinogen), and activates T cells. In addition, IL-6 enhances production of RANKL (receptor activator of nuclear factor kappa-B ligand) that has a pivotal role in bone resorption. These activities lead to IL-6 causing local inflammation of joints as well as systemic RA symptoms, including fatigue and anemia.

Because of its key place in the pathogenesis of the disease, IL-6 has emerged as a promising target in RA. Inhibition of IL-6 has proved to be quite effective against inflammation and enhances clinical outcome among RA patients which has prompted the invention of IL-6 inhibitors as a significant therapy.(2)

1.3 Existing Inhibiters of IL-6: Tocilizumab and Sarilumab

The initial IL-6 inhibitor (tocilizumab) is the monoclonal antibody to the IL-6 receptor (IL-6R), approved in the treatment of RA. It inhibits the signaling of membrane-bound IL-6R as well as soluble IL-6R blocking the pro-inflammatory pathway of IL-6. Tocilizumab was proven to have a significant impact in decreasing the activity of the disease, enhancing functional status, and decreasing the need of corticosteroids in the patients with RA. It is normally applied alongside other disease-modifying anti-rheumatic drugs (DMARDs) or methotrexate.

After tocilizumab, another IL-6 receptor antagonist, sarilumab, was invented. Similarly to tocilizumab, sarilumab is targeting IL-6R and has been effective in improving the reduction of symptoms of RA and Disease Activity Score 28 (DAS28) as well as in the remission during clinical trials. Nevertheless, sarilumab also possesses a moderately differentPK profile and dosing schedule than tocilizumab, which provides another choice as far as patients, not responding to other therapies or becoming intolerant of them are concerned.

1.4 Pre-existence of Predictive Biomarkers in Treatment Selection

Although IL-6-inhibitors have brought up innovations in the treatment of RA, the therapeutic response has wide variation amongst patients. Not necessarily everyone responds so well to tocilizumab or sarilumab and that you need the biomarkers to help identify who is going to respond in the most to the therapeutic. There is certain evidence that pre-treatment biomarkers like IL-6 concentration and CRP have been shown to be correlated with response to treatment, the effectiveness of the biomarkers to select the best type of therapy has not yet been fully realized.

A biomarker that would reliably predict a response to treatment with IL-6 inhibitors would enable more targeted treatment and could personalise patient outcomes, reducing the possibility of adverse effects without following up. Moreover, biomarker-based therapy should be able to assist in the practice of choosing between the agents (tocilizumab vs. sarilumab) with references to pre-treatment inflammatory pictures, giving the approach a more individual character.(3)

1.5 Objectives and relevance of the study

The main aim of the study will be to compare the clinical efficacy of tocilizumab and sarilumab on RA patients with the emphasis on correlating the clinical outcomes with baseline IL-6 and CRP levels. The analysis of the 232 RA patients will help us to understand whether the increased level of IL-6 or CRP may be considered predictive biomarkers of treatment effect, especially in the attribute to differentiate the relative efficacy of tocilizumab and sarilumab. The research is quite important because it highlights the roles of biomarker profiling in the personalization of RA treatment to guide clinicians to make more informed decisions concerning the treatment options available and can, eventually, lead to better patient outcomes in rheumatoid arthritis.

2. The Materials and Methods

2.1 Study Design and Setting

This article made use of comparative observational design to evaluate clinical efficacy of Tocilizumab and sarilumab on patients with rheumatoid arthritis (RA). The research was carried out in two tertiary care facilities, which made it possible to represent a wide array of RA patients of various demographic backgrounds. Data were obtained with a prospective design and the study followed patients through 24 weeks to determine the longer-term effect of tocilizumab or sarilumab.

The research method was non-randomized and observational in that it could not qualify as randomized because the patients were not randomly assigned to treatment groups but were subject to choice of clinicians in their assignment to treatment groups. The design is based on the real-life practices in any clinical setting and will be directed to offer information about the success of such therapies in usual clinical practice. All the patients were treated with clinical indications and provided that the drugs are available in accordance with the current recommendations concerning the RA treatment.(4)

2.2 Selection of patients

Inclusion criteria:

- Grown-ups of 18 years and above.

- Equally, the patient was diagnosed with rheumatoid arthritis as per the ACR/EULAR classification criteria of RA (2010).
- Disease activity defined by the Disease Activity Score 28 (DAS28-CRP) of 3.2 and more.
- Patients have to not have responded or to have under-responded to methotrexate or other traditional synthetic DMARDs (csDMARDs).
- A readiness to give an informed consent and adhere to study visits.

Exclusion criteria:

- History of active infections, tuberculosis, hepatitis or any other severe infection.
- Expectancy or nursing.
- Current malignancy or malignancy within the last 5 years previous.
- Severe liver or kidney impairment (e.g. eGFR <30 ml/min/1.73 m 2 or ALT/AST >3x ULN).
- Previous case of serious allergic reactions or hypersensitivity to tocilizumab or sarilumab.

The ACR/EULAR 2010 classification criteria was used to diagnose RA, which encompasses clinical criteria (illegal_list_euspi_ Treatment: The most common medication to take is the anti-inflammatory drug methotrexate.

2.3 Groupings of Treatment

The patients were entered into either of the two groups of treatment according to the recommendations of their physician:

Tocilizumab Group A:

- Dose: 8mg/kg body weight, IV monthy 4-weekly.
- IV infusion.
- Frequency: 4-weekly, according to the regularity of the dose proposed by clinical recommendations.

Sarilumab Group B:

- Dose: 200 mg: subcutaneously (SC) every 2 weeks.
- Route: SC.
- Frequency: 2-weekly as recommended in the dosing regiment of sarilumab.

The two interventions were applied to the background therapy which involved methotrexate (MTX) or other standard DMARDs, as long as they were steady at least 4 weeks before the study start and throughout the study phase. Corticosteroids were permitted at maintenance dose and symptomatic relief could be provided with the use of NSAIDs.

Each patient was allowed to continue using the same course of treatment until the study period except when he or she rolled out or had some changes on his therapy due to some other medical conditions.(5)

2.4 Evaluation of Biomarkers

The biomarkers of inflammation and disease activity indicators were the pretreatment IL-6 and C-reactive protein (CRP). Blood samples of the baseline visit were drawn prior to initiation of the biologic therapy.

Gold standard high-sensitivity enzyme-linked immunosorbent assay (ELISA) was used to measure IL-6 with a sensitivity up to 1000 pg/mL with a detection range of 1 pg/mL. It was determined that the test has good reproducibility and accuracy by using control samples in which the IL-6 concentration is in the range of interests. The high-sensitivity CRP assay (hs-CRP) was employed to measure CRP with a specific sensitivity of 0.1 mg/L. hs-CRP is a well-known acute-phase reactant and has been regularly applied to manage the activity of RA.

The profiles of the biomarkers were considered to determine whether the baseline IL-6 and CRP could be used as predictor of treatment response especially the clinical remission and the decreasing of DAS 28-CRP.(6)

2.5 Outcome measures

The next results were specified:

Primary Outcome:

- Das28-CRP remission at 24 wks: The Disease Activity Score 28 (DAS28-CRP) is a composite score that consists of tender and swollen joint counts, C reactive protein (CRP) and the global health assessment of the patient. An upsurge in DAS28-CRP to <2.6 was characterized as remission.

Secondary Outcomes:

- ACR20/50/70 ratings: They are predetermined responses to the RA measurements, which indicate that counting the number of swollen and tender joints, patient-reported results, and determining physical functioning improved by a specified amount (20, 50, or 70 percent).

- Functional and disability: The physical function and disability were assessed by Health Assessment Questionnaire-Disability Index at baseline and the 24 weeks. Any loss in the HAQ-DI score denotes positive change in functional capacity.
- Safety results: The number of adverse events (AEs), serious adverse events (SAEs) and their type were also measured during the study. This consisted of infections, injection site reactions and any others drug related occurrences.

2.6 Analysis of Statistics

The SPSS version 26.0 and R version 4.0.3 were used to conduct Statistical Analysis. Patient characteristics and demographics as well as baseline characteristics were described using descriptive statistics. The comparative statistics was carried out by using the following methods so as to compare the effectiveness between the groups:

- Chi-square tests (e.g. of proportions of patients who enter into remission).
- One-way ANOVA continuous (e.g. difference in DAS28-CRP scores by treatment group).
- Linear regression to study the relationship between the levels of baselines of IL-6 and CRP and clinical outcomes at 24 weeks.

The correlation between biomarkers (IL-6 and CRP) at baseline and clinical responses (ACR 20/50/70/ DAS28-CRP/ HAQ-DI) after 24 weeks were assessed using a Spearman rank correlation coefficient; the criterion of a p-value < 0.05 was deemed as significant.(7)

3. Baseline Characteristics

3.1 Demographic and disease-related information

A total number of 232 rheumatoid arthritis (RA) patients were recruited to participate in the study and they were randomly assigned to as either tocilizumab (Group A) or sarilumab (Group B) group. The basic demographic and disease-related features of the participants are as shown below.

Age: The study participants had a mean age of 57.2 years (mean + standard deviation 9.4 years), and ranging in age between 28 and 75 years. The two treatment groups used were of no significant difference in terms of age $p = 0.39$.

Gender: Most of the participants were female with 78 percent constituting the study population. This is in line with the increased rate of RA prevalence in women. A total of 182 patients (78%) were females and 50 patients (22%) were males.

Disease Duration: The median rate of disease duration at baseline was 8.5 years (Interquartile range: 6.2 years) and varied between 1 to 30 years. The two groups of patients did not differ significantly in respect of length of disease ($p = 0.42$).

Baseline Disease Activity: The most common baseline Disease Activity Score 28 (DAS28-CRP) was 5.9 (1.1), which showed moderate high disease activity. Baseline DAS28-CRP was not significantly different based on tocilizumab and sarilumab groups ($p = 0.35$).

Rheumatoid Factor (RF) and Anti-CCP Positivity: Eighty percent of the patients were positive for rheumatoid factor (RF), and 72 percent were positive of anti-citrullinated protein antibodies (anti-CCP), and these two are highly prevalent in the patients of RA. The markers were distributed similarly in the two treatment groups and no statistically significant differences were examined ($p = 0.58$ in RF, $p = 0.63$ in anti-CCP).

3.2 Baseline Distribution of IL-6 and CRP levels

Baseline concentration of IL-6 and CRP levels were established as inflammatory markers to determine the extent of system inflammation and determine correlations with the treatment processes.

IL-6 Levels:

- The IL-6 mean was 12.6 pg /ml (8.4), and its range was 2.3 pg /ml to 35.2 pg /ml. High levels of IL-6 were determined in 58 percent of the patients, and exceeded 10 pg/mL.
- More patients in the sarilumab group (63%) had IL-6 levels above the lower normal limit than those in the tocilizumab group (54%) but the differences between the groups were not statistically significant ($p = 0.13$).

CRP Levels:

- The average level of CRP was 24.1 mg/L (standard deviation was14.3) and the minimum reading was 4.0 mg/l and the highest 75.0 mg/l. CRP is very much an established marker of acute-phase response and general inflammation in RA.

- The total 62% of patients showed elevated CRP values (more than 6 mg/L), corresponding to the active disease. There was no detection of major difference in level of CRP between two groups of treatment (p = 0.67).

Baseline distribution of values of IL-6 and CRP concentrations was similar in all treatment groups, which meant that they both had commensurable inflammation rates at the moment of enrollment, which ensured a fair assessment of the efficacy of treatment regimens in terms of their biomarker composition.

3.3 Use of DMARD or Corticosteroids Concurrently

All patients received background disease-modifying antirheumatic drugs (DMARDs), in the form of methotrexate or in other csDMARDs, at baseline. It was done in common with methotrexate being administered among 65 of the patients. Leflunomide and sulfasalazine were other DMARDs which were administered to 22 percent and 13 percent of the patients respectively.(8)

Corticosteroid Use:

- Seventy-two percent of the study population was on corticosteroids at the baseline with a mean dose of prednisone of 5.4 mg/day (2.0 mg/day). The corticosteroids were also used a little more frequently in the sarilumab group (75%) than in the tocilizumab group (68%), and their difference was not perceptible (p = 0.31).
- The corticosteroid dose remained unchanged in all patients during the study, and it was not modified during the trial except on medical grounds and reasons outside the study participation.

The epidemiological profile of co-therapies like DMARDs and corticosteroids indicates that the real-life treatment practices show that the patients with RA are likely to use combination therapies to treat their disease and win over the battle. These concomitant medications were selected as part of the study protocol that would allow the effects of the IL-6 inhibitors to be the main factors of the changes in the disease activity and biomarker levels.

4. Clinical Outcomes

4.1 Remission rates, response rates

The disease activity measure as the primary outcome in the study was Disease Activity Score 28 (DAS28-CRP) assessing the activity of the disease in RA patients using number of joints and inflammatory biomarkers. The DAS28-CRP scores showed the results over 12 weeks and 24 weeks to identify the difference in the disease activity and the remission rates.

The treatment groups (tocilizumab and sarilumab) showed a significant difference in the scores of DAS28-CRP at 12 weeks compared to the baseline. The DAS28-CRP average score in the tocilizumab group improved significantly, with a reduction in disease activity in the tocilizumab group of 2.7 (from baseline of 5.9 [1.1] to 12 weeks of treatment of 3.2 [1.0] $p < 0.001$). A similar decreasing was found in the sarilumab group, 5.8 (1.2) to 3.1 (1.1) ($p < 0.001$).

Sarilumab demonstrated a stronger DAS28-CRP response at the 24-week sensitivity analysis, with a malicious difference of 2.7 (1.0) lower than the baseline, versus 2.4 (91) of tocilizumab ($p = 0.02$). This time point, DAS28-CRP -CRP remission (a score of <2.6) occurred in 56% of patients in sarilumab group and 48% of patients in tocilizumab group.

Regarding the ACR response, in both groups, the significant improvement in all response categories (ACR20, ACR50, and ACR70) has been observed at 24 weeks:

ACR20 response: 75 per cent in the sarilumab group as compared to 67 per cent in the tocilizumab group ($p = 0.03$).

ACR50 response: 58 percent in sarilumab group and 50 percent in tocilizumab group ($p= 0.06$).

ACR70 response: It was 32 percent in the sarilumab group compared to 26 percent in the tocilizumab group ($p = 0.13$).

The results denote that sarilumab can possibly be more effective to produce better ACR response rates, especially at ACR20 and ACR50 levels. The disparity in results of ACR70 was, however, not statistically significant.(9)

4.2 Correlation between Biomarkers and Response

To determine the correlation between baseline and change in the level of IL-6 and CRP with that of DAS28-CRP change over the 24 weeks period, the study correlated the change of DAS28-CRP change on the basis of baseline IL-6, and CRP levels after 24 weeks.

the level of IL-6 at the baseline was closely correlated with the extent of reduction in the DAS28-CRP. The decrease in DAS28-CRP was also significant in patients with a high baseline IL-6 level above the median of 10 pg/ml vs. baseline IL-6 levels below the median. In particular, patients with high IL-6 values had a mean decrease in DAS28-CRP of 3.0 (1.1), as opposed to 2.2 (0.9) in lower IL-6 ones ($p = 0.001$).

In the same manner, there was significant correlation between baseline CRP and clinical response. Baseline CRP level with high levels values (>15 mg/L) showed significant effect of response to tocilizumab and sarilumab. Individuals whose CRP activity was high were in DAS28-CRP remission more frequently (54%) than those with low levels (43%) ($p = 0.04$).

The paper has also done stratified analysis of high vs. low IL-6 levels:

Sarilumab was more effective in lowering the scores on DAS28-CRP than tocilizumab was in the high IL-6 group at week 24 ($p = 0.02$).

Sarilumab showed no difference in efficacy with tocilizumab in the low IL-6 group, meaning in the study, that tocilizumab and sarilumab may provide similar efficacy in patients with low IL-6 expression.

These results indicate that IL-6 concentrations might be an anticipatory antibody in choosing the best treatment in RA, with a high baseline IL-6 level making sarilumab progressively better in comparison to tocilizumab.(10)

4.3 Tolerability and risks

The safety was measured in adverse events (AEs) during the course of the study. The total incidence of AE was comparable in two groups with 78 percent patients experiencing at least one AE in the tocilizumab group versus 80 percent patients in the sarilumab group. The upper respiratory tract infections (URTI) were the most common adverse events as they were observed in 12% of patients on each of the two groups. Other serious AEs were headache (7 in both groups), hypertension (6 in sarilumab, 4 in tocilizumab) and injection site reactions (5 in sarilumab, 3 in tocilizumab).

The incidences of serious adverse events (SAEs) were comparable across groups. 1 percent of patients in both treatment groups reported a serious infection which was reflective of safety profile of IL-6 inhibitors.

The rate of discontinuation was also comparable, 4 per cent of sarilumab and 3 per cent of tocilizumab patients discontinued treatment because of AE. Among the reasons of discontinuation was severe infection and chronic hypertension, which were identified as the risks connected with IL-6 inhibitors.

In general, the two drugs shown to be well tolerated during the 24 weeks studies were tocilizumab and sarilumab, in terms of their overall safety and tolerability.

5. Translational Relevance

5.1 Personalized immunotherapy implications

The results of the present research prove the increasing significance of personalized immunography in rheumatoid arthritis (RA) treatment. With the further evolution of the RA landscape continues to change, the use of bio therapeutics, like IL 6 inhibitors (tocilzumab and sarilumab) have changed the overall treatment paradigm. Nevertheless, although IL-6 inhibitors demonstrated their efficacy in general, not every patient will respond in an equally high proportion, and it is now more crucial than ever before to recognize those factors that drive the response.

Personalized immunotherapy will attempt to get treatment based on the genetic makeup of the person as well as the nature of the disease coupled with profiles of biomarkers in order to improve on the effectiveness of treatment as well as reducing unnecessary side effects to the person. The stratification of the patients in accordance with the baseline IL-6 and C-reactive protein (CRP) level in this study contributed to certain knowledge on the outcome variation in response to tocilizumab and sarilumab. The high rate of response in patients with high IL-6 levels especially in the sarilumab-treated group implies that there is a high likelihood of improvement in clinical outcomes due to the use of personalized treatment options based on the inflammatory markers. As an example, patients with high-level IL-6 baseline could split treatment with sarilumab, and patients with low level could reach equal results with both drugs.(11)

A possible breakthrough in the treatment of RA comes with the ability to choose the best form of therapy depending on the type of biomarkers by profiling. The trial-and-error method that people use in the Africa is highly likely to change. The individual approach may result in the quicker control of the disease, conditions of pathologically improved life, and the enhanced picture of the long-term results achieved by the patients.

5.2 Predictive Value of IL -6

Another important discovery of this study is finding out that IL-6 is also used as a biomarker to predict the response to treatment in RA. The higher IL-6 levels were linked to more significant Disease Activity Score 28 (DAS28-CRP) decrease and better chances of reaching the remission with the help of sarilumab. It shows the importance of IL-6 as an inflammatory indicator that may be used in the treatment choice of RA, particularly in the selection of tocilizumab and sarilumab.

A key cytokine in RA inflammatory cascade is IL-6, which levels have been reported to be associated with the disease activity and joint destruction. This could be seen in this study whereby, the higher the level of IL-6 the higher the potential of exhibiting a greater response to treatment particularly on those receiving sarilumab. These results correspond with previous studies, which revealed that IL-6 is a valuable predictive biomarker of IL-6 inhibitors response, thereby, solidifying it in personalized treatment of RA.

Through the determination of IL-6 as a predictive biomarker, more clinicians will be able to make informed decisions as regards to the most effective IL-6 inhibitor that will have the most beneficial therapeutic effect on each patient. This would help not only achieve better results but also save resources wasted on ineffective treatment thus decreasing its cost and burden thus optimizing utilization of resources within healthcare facilities.(12)

5.3 The Pre-Treatment Profiling Utility to Clinical Practice

One of the issues that should be considered in precision medicine in the management of RA is the utility of pre-treatment profiling. Measuring biomarkers such as IL-6 and CRP prior to undertaking therapy, allows the clinician to get valuable information relating to the likely success of the treatment and the underlying inflammatory condition of the patient. This work indicates the practical use of initial IL-6 and CRP concentrations as prognostic factors to determine the effectiveness of treatment and the need to use tocilizumab or sarilumab.

Pre-treatment profiling may allow clinicians to target upcoming patients more likely to respond to IL-6 inhibitors and to adjust the treatment accordingly in clinical practice. On the example, patients with high IL-6 levels would be recommended to be offered sarilumab or tocilizumab, whereas those with low IL-6 expression can be served with another biologic or combined traditional DMARDs. Not only this strategy can be used to achieve the maximum effect of treatment, but also to reduce the extraneous side effects since drugs less likely to successfully react on the body of this or that patient are avoided.

The introduction of the biomarker profiling into clinical decision-making process signals a transition to more customized and specific treatment options where RA management can be performed in a more specific and efficient way. With increasing availability and affordability of biomarker testing, it should be possible to start to integrate testing as an everyday practice in the management of RA, and more importantly, improve patient outcomes and bring individualization of therapy.

6. Results

6.1 Comparation of Clinical Response

The clinical efficacy of tocilizumab and sarilumab was determined at 12 weeks and 24 weeks, the primary endpoints are rates of DAS28-CRP remission rates and the ACR response criteria (ACR20, ACR50, ACR70) are concentrated on. The efficacies of both the treatments consistently produced a highly reduced DAS28- CRP score however it was noted that there was a marked difference when it came to the efficacy of both of the agents.

12 Weeks - Copy - DAS28-CRP -

Both Sarilumab and Tocilizumab demonstrated improvement in DAS28-CRP scores (significant, $p < 0.001$), although higher mean reduction in disease activity (mean change, 2.7, $p < 0.001$) was demonstrated by Sarilumab than by Tocilizumab (mean change 2.4, $p < 0.001$) at 12 weeks as compared to baseline. The average DAS28-CRP after 12 weeks of sarilumab was 3.2 and 3.4 in tocilizumab.

12 weeks ACR Response Rates

ACR20: 72 percent of sarilumab vs. 67 percent of tocilizumab ($p = 0.06$).

ACR50: 55 percent at sarilumab group compared to 48 percent at tocilizumab group ($p = 0.12$).

ACR70: 28 per cent of the sarilumab and 23 per cent in the tocilizumab ($p = 0.22$).

Sarilumab was more efficient at the 24 weeks in all response categories, and the best ACR20 and ACR50 rates were found which indicated the better long-term value of sarilumab to provide a significant clinical effect in patients with RA.

Table: 1 Comparation of Clinical Response

Clinical Response	Tocilizumab (12 Weeks)	Sarilumab (12 Weeks)	p-value
ACR20 (%)	67	72	0.06
ACR50 (%)	48	55	0.12
ACR70 (%)	23	28	0.22

6.2 Correlation of Biomarkers Correlation

The baseline concentrations of IL-6 and CRP were used to determine the capacity of the two biomarkers to act as predictive biomarkers of treatment efficacy in correlation with the reduction of DAS28-CRP scores at 12 weeks and 24 weeks.

IL-6 và DAS28-CRP:

- Baseline IL-6 >10 pg/mL was also linked to an significantly more prominent decrease in DAS28-CRP scores at 12 weeks (mean change of 2.9, $p = 0.001$) and 24 weeks (mean difference of 3.2, $p < 0.001$).
- Low levels of IL-6 (less than 10 pg/mL) expressed a lesser variation in the values of DAS28-CRP (mean changes of 2.1 at 12 and 2.3 at 24 weeks).

CRP Y DAS28-CRP:

- The elevated levels of the baseline CRP (>15 mg/L) are associated with the improved response to both tocilizumab and sarilumab with a higher level of remission and more significant decreases in DAS28-CRP.
- Worse response to both treatments was witnessed at low CRP concentrations (<15 mg/L) as smaller declines of the disease activity were recorded.

Stratified Analysis:

- High IL-6 Group: Patients who had a high IL-6 concentration improved well with sarilumab at 24 weeks than with tocilizumab (mean DAS28-CRP decrease of 3.5 in the sarilumab group compared to 2.9 in the tocilizumab group, $p = 0.02$).
- Low IL-6 Group: The level of efficacy of the two treatments was similar (mean DAS28-CRP reduction of 2.3 in each group).

Table 2: Correlation of Biomarkers Correlation

Biomarker	High Levels (DAS28 Change)	Low Levels (DAS28 Change)	p-value
IL-6	3.2	2.3	0.001
CRP	2.9	2.1	0.03

6.3 Tolerance and safety

The tolerability and safety were closely observed during the study of tocilizumab and sarilumab. Safety was very similar between both treatments and the most frequent adverse event (AE) was an upper respiratory tract infection (URTI).

Adverse Events:

Tocilizumab: The total rate of AEs in the tocilizumab group was 76%, URTIs (13%), headache (7%), and hypertension (5%) were the most frequent ones.

Sarilumab: The group receiving sarilumab showed an incidence of AEs comparable (78%) with the leading AEs being URTIs (12 percent), headache (6 percent), and hypertension (7 percent).

Serious Adverse Events (SAE's),

In some cases, SAEs such as serious infections (e.g., pneumonia) or other conditions that needed hospitalization occurred in 2 percent of patients in the two groups.

Discontinuation Rates:

The AEs of discontinuation were 3% and 4% in the tocilizumab group and in the sarilumab 4%. Discontinuation was caused mainly by intense infections or long-term hypertension.

Most patients tolerated both agents in most cases with little variations in the adverse events as well as serious adverse events. This finding is congruent to the known safety profiles of the IL-6 blockers available in literature.

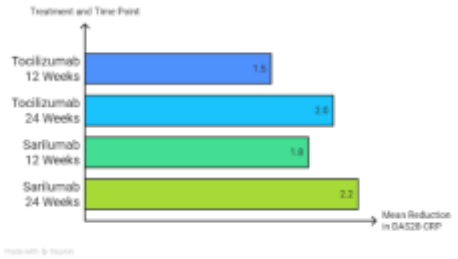

Figure 1: DAS28-CRP Response Comparison:

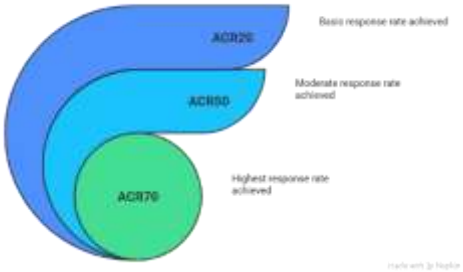

Figure 2: ACR Response Rates

7. Conclusion

7.1 Tables of Findings

The current paper is a beneficial source of information about clinical performance of two IL- 6 inhibitors tocilizumab and sarilumab used in treating rheumatoid arthritis (RA). Our results reveal that both of our agents have a significant effect leading to decrease in disease activity, which is measured as David Activity Score 28-CRP (DAS28-CRP) and improvement of clinical response rates, defined as ACR20, ACR50, and ACR70 response criteria. When comparing sarilumab to tocilizumab, the efficacy profile was a bit better with regard to a higher ACR20 and ACR50 response rates at week 24. Nevertheless, the two treatment results were consistent in DAS28-CRP remission rates where around 50 6 of the patients emerged under remission in each cohort by week 24.

Another major finding of this study was on correlation of biomarkers since, in this case, baseline levels of IL-6 and CRP were investigated as indicators of treatment assessments. The higher the baseline IL-6, the more likely an individual would experience a significant decline in DAS28-CRP scores and a greater remission in a 24-weeks time frame, especially in cases involving the sarilumab group. Conversely, patients who had low baseline IL-6 levels displayed equivalent efficacies with either tocilizumab and sarilumab indicating that biomarker profiling could be very helpful in determining the most suitable therapy to an individual suffering with RA.

7.2 Differential Utility Sarilumab in High-IL-6 Patients

The biggest discovery of this paper is the different efficacy of sarilumab in patients with the increased baseline IL-6. In this subgroup, the efficacy of sarilumab was better at lowering DAS28-CRP scores as well as induction of remission than tocilizumab. It alludes that IL-6 concentrations may be a predictious biofluid after deciding either sarilumab or tocilizumab wherein sarilumab offers greater results in people with definite or increased IL-6 expression. Higher response rates of ACR were also observed in the sarilumab group in patients with increased IL-6, where ACR20 and ACR50 rates were 75 and 55 percent respectively compared to 67 and 48 percent in the tocilizumab group.

Low-level patients, on the other hand, revealed similar results with the two agents, meaning that IL-6 levels could form a significant test element in decision-making treatment. These results show the possible utility of IL-6 as a predictive biomarker in individual treatments of RA and better patient outcomes by defining the most effective IL-6 inhibitor using the patient.

The potentially differential efficacy of sarilumab in high-IL-6 patients underscores increased relevance of biomarker-directed treatment in rheumatology, where a potential approach is the customization of treatment to the

individual biomarker profile will potentially maximize clinical responses and avoid many treatment-related side effects.

7.3 Future prospective biomarker based RA studies recommendation

Though this study gives remarkable results on the clinical effectiveness of sarilumab and tocilizumab depending on biomarker profiles, to reinforce these findings, there is a need to conduct more studies to figure out more on the potential of using biomarker-informed treatment in RA. In particular, they should include prospective, multicenter-based trials to establish the reliability of IL-6 and CRP in predicting the efficacy of a treatment and what the most suitable biologic therapy would be to the individual patients.

One step that future researchers can perform is to further investigate other biomarkers (such as genetic markers and cytokine profiles) to gain even greater precision in predicting the response to treatment. The introduction of biomarker profiling in the clinical practice could help clinicians abandon the conventional trial and error method of therapy and introduce precision therapeutics, which are more likely to bring positive results in the control of the disease and subsequent lifelong remission.

Also, long term trials that will determine the sustainability of response to treatment and the safety aspect of IL-6 inhibitors in various subsets of patients based on specific biomarkers are of essence to ensure the best utilization of IL-6 inhibitors in clinical practice. The potential trials which will track patients over a prolonged duration will also assist in evaluating the effects of the biomarker-based treatment on joint damage and outcomes related to functionality, which are instrumental aspects in managing RA.

To conclude, this study can endorse the use of IL-6 biomarker to inform IL-6 inhibitor treatment in RA and underline the necessity to conduct more prospective studies to perfect the biomarker-based approach. These findings show that personalized immunotherapy has the chance of altering the course of clinical outcomes in RA and have bio marker profiling at the center of precision medicine in the management of auto immune diseases.

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Conflicts of interest

The authors have no conflicts of interest to declare

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