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Research article

Effect of Different Rheumatoid Arthritis Medicines on the Disease Activity Score (DAS) 28 in the Patients with RA Suffering from Bacterial Urinary Tract Infection.

Rusul Hisham Ahmed[1]*

ABSTRACT

Rheumatoid arthritis (RA) is one of the most impact autoimmune diseases in society, as it affects the movement and work of people. There are different types of medications given to patients with RA. The current study aims to fill the knowledge gap related to the effect of urinary tract infection (UTI) caused by bacterial pathogens in people with RA who have taken different types of medications on the activity of the disease in terms of disease activity score (DAS) 28. In the present study, The 100 cohorts included 30 healthy control volunteers and 70 RA patients divided into two groups, The first group contained 41 patients (24 female and 7 male) with RA and UTI; the second group, 29 patients suffering from RA (24 female and 5 male) without suffering from UTI. The study showed that there is no change in the level of disease activity DAS28 in the patients with RA getting different RA medicines (1. Enbrel and Methotrexate, 2. Enbrel, 3. Methotrexate, 4. Humira and methotrexate, 4. Rituximab) and their urinary tract infected with different bacteria as compared with DAS28 of RA patients using above medicine and did not suffer bacterial UTI. ($P>0.05$). No effect of the type of medicine on the DAS28 in each patient group. It was concluded for the first time that the RA medicines do not affect the activity of RA (DAS28) in patients with RA and suffering from UTI or not suffering from UTI.

Keywords: Bacterial infections, Biological therapy, Rheumatoid arthritis, Urinary tract infection.

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a progressive inflammatory and autoimmune disease with unknown etiology. It affects 0.5-1% of the world population, and disease characteristics include synovial inflammation and hyperplasia, degradation of cartilage and bone, autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein (ACPA) production, and various systemic characteristics such as cardiovascular, pulmonary, psychological and skeletal disorders [1]. The pathogenesis of RA is complex and requires large numbers of different types of cells and signaling pathways. it is generally believed that autoimmune mechanisms and cytokines play a role in the onset and progression of the disease [2]. Tumor necrosis factor (TNF), and Interleukin (IL)-1 are pro-inflammatory cytokines and the best studied among these and are discussed further in this study.

* Correspondence: **Rusul Hisham Ahmed**. E. mail: rusul.ahmed1202@sc.uobaghdad.edu.iq
Al-Kindi Hospital, Ministry of Health, Baghdad, Iraq.
Full list of author information is available at the end of the article.

Urinary tract infection (UTI) is the most frequent bacterial infection that affects millions of people annually. Infection-induced inflammation of the urethra, urinary bladder, and kidneys. The presence of elevated levels of bacteria in the urine (bacteriuria) is diagnosed with concomitant urination. Pyelonephritis signs include bacteriuria and pyuria in the presence of (white blood cells in the urine). UTI can be described as difficult or uncomplicated. The UTI is considered uncomplicated if cystitis or pyelonephritis occurs in an otherwise healthy person (premenopausal and non-pregnant women) and no anomalies are present in the urinary tract [3].

Treatment of patients with RA is aimed at relieving pain and reducing inflammation, and the ultimate objective for all patients is to reach recovery or at least low disease activity. In this sense, 10 international guidelines have been collected by the European League Against Rheumatism (EULAR) on how to treat patients [4]. There are several medicines used in treating RA i.e. Methotrexate (MTX): Methotrexate (MTX) belongs to a class of medications known as antimetabolites and is widely used to treat many autoimmune disorders, such as RA, SLE, and rheumatic polymyalgia [5]. ENBREL is a TNF Inhibitor and reduces signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA. ENBREL can be initiated in combination with methotrexate (MTX) or used alone. The most popular biologic form used to treat patients with RA who do not respond to methotrexate (MTX) or other disease-modifying anti-rheumatic drugs are TNF-α inhibitors (DMARDs). TNF alpha inhibitors include infliximab, certolizumab pegol, etanercept, golimumab, and adalimumab [6]. HUMIRA is a prescription medicine used alone, with methotrexate, or with certain other medicines to reduce the signs and symptoms of moderate to severe RA in adults, and may prevent further damage to your bones and joints. It is a TNF blocker medicine that can lower the ability of your immune system to fight infections. Rituximab is a monoclonal antibody (mAb) that targets the CD20 antigen; it depletes B cells and is used as a therapeutic biological agent in rheumatoid arthritis (RA) [7].

The present study aims to evaluated the effect of the kind of medicine that patients of RA receive (who either infected or not infected with pathogenic bacteria) during the duration of treatments on the disease severity in terms of disease activity score (DAS 28).

2. MATERIAL AND METHODS

2.1. Patients' samples

The 100 cohorts in the current investigation included 30 healthy control volunteers and 70 RA patients divided into two groups, The first group contained 41 patients (24 female and 7 male) with RA and UTI; the second group, 29 patients suffering from RA (24 female and 5 male) no UTI was identified. The patients were indoor patients receiving treatment and medicine at Baghdad Teaching Hospital in Baghdad, Iraq, and 30 healthy cohorts were recruited from regular hospital visitors and regular employees of the University of Baghdad in Baghdad, Iraq. Rheumatologists in specialized hospitals adhered to 2010 RA classification standards [8]. The patients hadn't used any corticosteroids or disease-modifying medications in the month before the current study's time point. There were 59 female and 11 male RA patients, with a mean age of 47.1 years (mean + SD), disease activity score 28 (DAS28) [10] of 4.88±0.94 (mean SD), and IgM rheumatoid factor positivity of 52.8% and anti-CCP positivity of 71.4%, respectively. The levels of DAS28 were measured using the accepted techniques described by Prevoo et al. (1995) and Carpenter et al. (2018) [9].

2.2. Laboratory bacterial examination

A hundred cohorts provided a urine sample, which was then promptly transferred to the lab to be inoculated onto the proper medium using sterile screw cups. The urine samples were inoculated onto MacConkey agar and incubated at 37°C for 18 h to check the lactose fermentation of isolates, as well as onto blood agar for the purpose of identifying the kind of hemolysis. Under sterile and aerobic circumstances. The selected colonies were re-cultured on mannitol salt agar to identify the staphylococcus species. By doing Gram staining, where a single colony of each isolate was picked up and stained in accordance with the normal methodology and examined under oil immersion for comparable types of cells, the morphological identification of the isolates as bacilli was verified microscopically. Gram stain, growth characteristics, and other biochemical test procedures were used for bacterial identification [10]. For each isolate, the Gram stain slides were created using the Gram stain kit in accordance with the standard Gram stain protocol. This stain is often the first differential test for bacterial identification according to the bacterial cell shape and the stain color [11]. Pure isolated colonies of bacteria were kept for a short time (2 weeks) by culturing on the nutrient agar plate and storing at 4 ^{o}C/ While for medium-term (a month) the pure culture of bacterial isolates was cultured onto nutrient agar slant (sterile tube) and kept at 4 ^{o}C. In order to keep bacteria for a long time, pure colonies were cultured at 37 °C for 24 h into the nutrient broth that included 15% glycerol and then stored at -20 °C for a year.

2.3. Experiment

In the present study, the DAS28 was calculated in two patient groups (RA+UTI and RA without UTI) who were taking different medicines [1. Enbrel and Methotrexate (50 mg/ week), 2. Enbrel (50 mg/ week), 3. Methotrexate (25 mg), 4. Humira (40 mg/ week) and methotrexate (25 mg/week, 4. Rituximab (500 mg/week)] and a healthy control group. The purpose of the present experiments is to check the effect of different medicines on the disease activity in terms of DAS28 of patients with RA either suffering from UTI or not.

2.4. Statistical analysis

All data represented in mean and standard deviation the ANOVA test was used to identify the significant difference between patients and control groups, a P value less than 0.05 was considered a significant difference.

3. RESULTS

3.1. DAS28 of patients with RA

The current study showed that the disease activity score (DAS) 28 in patients with RA is higher than its levels in healthy people, and this is logical because patients with RA suffer from joint symptoms and problems, which are related to determining the value of DAS28 (Fig. 1).

3.2. Effect of type of treatment on DAS28

In this study, the effect of different types of RA treatment on the level of disease activity score (DAS28) of RA disease was evaluated. The effect of different drugs was evaluated in two

groups of patients with RA. First group: Patients with RA and suffering from UTI. As for the second group, they are subjects with RA disease and do not suffer from UTI.

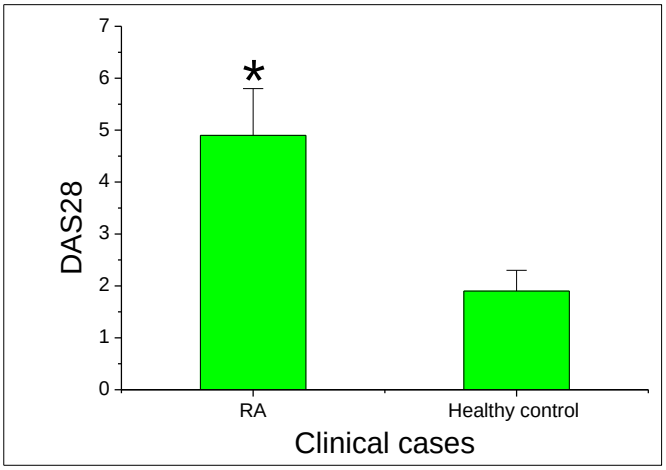

Fig. 1. Disease Activity Score (DAS) 28 score in groups of patients with rheumatoid arthritis (RA) and control. There is a significant difference between the patients group (RA) and healthy control group, (P>0.05).

The results showed that the use of different types of treatments and drugs had no effect on the level of disease activity of RA (DAS28) in both groups compared to the overall rate of disease activity (DAS28) in the urinary tract infection group and the group that did not experience UTI. This study proved that using different drugs to treat RA in the presence or absence of UTI has no effect on the DAS28 index on the other hand it does not affect disease activity either in the suffering from UTI or absence of UTI.

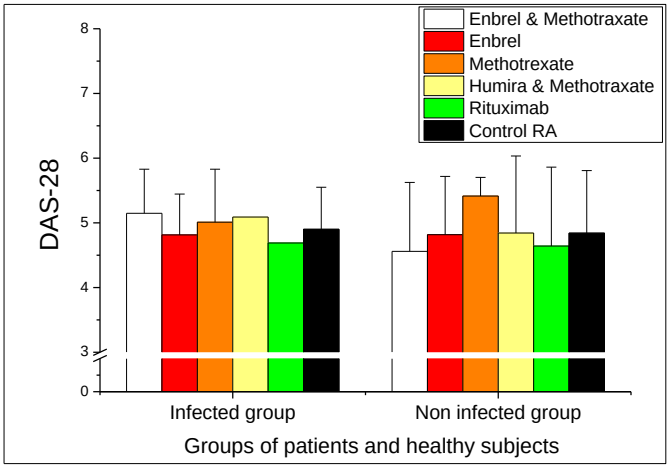

Fig. 2. Disease activity score (DAS) -28 in two groups of patients with RA disease. The patient's group suffering from RA and their urinary tracts infected with different species of bacteria and the patient's group suffering from RA (not suffering from bacterial UTI).

4. DISCUSSION

RA is an autoimmune disease. It occurs when the immune system mistakenly attacks healthy joint tissues, leading to inflammation and joint damage. The exact cause of RA is not well understood, but it is believed to result from a combination of genetic and environmental factors [12]. On the other hand, a UTI is a bacterial infection that affects the urinary system, including the bladder, urethra, and sometimes the kidneys. UTIs are caused by bacteria and are typically treated with antibiotics [3].

In the current study, it was found that the activity of RA (DAS28) is higher than the DAS28 in the healthy control group. It was also found for the first time that the activity of RA is not affected by the type of treatment that the patient uses, whether the patient suffers from UTI in addition to RA or suffers from RA only (without bacterial infection).

Mehta et al. (2019) found that patients with RA have a significantly higher risk of serious infections, particularly bacterial, respiratory, bloodstream, sepsis, skin, bone, and joint infections, which is greatest in those with higher disease activity [13]. Previous studies reported that common infections in the gastrointestinal and urogenital tract are associated with a lowered risk of RA, which contradicts the hypothesis that infections trigger the onset of RA [14]. Puntis *et al*., (2013) found a high correlation between incidences of UTI and suffering from RA. That happened because this group of patients (patients suffering from RA) use long-term oral steroids as sole therapy was associated with a high incidence of UTI and that was correlated with the duration of taking the anti-rheumatic drugs [15].

There is no direct link between bacterial infections like UTIs and the development of RA. However, some researchers have explored the idea that infections may trigger or exacerbate autoimmune diseases like RA in susceptible individuals. This is known as the "infection-triggered autoimmunity" hypothesis, and it suggests that infections could potentially contribute to the development of RA in genetically predisposed individuals. Infections can trigger autoimmunity by enabling the presentation of self-antigens, leading to the generation of autoreactive T cells that promote auto-inflammation and autoantibody generation. Still, the exact mechanisms behind this potential relationship are not fully understood, and more research is needed in this area [16].

Several previous studies by Pavelka et al. (2013) showed that in patients with moderately active RA in Central and Eastern Europe, induction therapy with Enbrel (ETN) and Methotrexate (MTX) led to DAS28 LDA, remission, and improvements in patient-reported outcomes (PROs) [17]. Fanouriakis et al. (2018) reported that in early arthritis patients, failure to fully implement the treat-to-target strategy could account for the low remission rates, despite significant reductions in DAS28, with DAS28 at three months being the most powerful predictor of suboptimal disease outcome during a 2-year follow-up in early RA [18]. There is no previous study highlighting the effect of suffering from RA and UTI in patients with RA under treatment with different medicines on the level of DAS28. That is why, the present study is the global pioneer study in this area.

5. CONCLUSION

It was found for the first time that the RA medicines do not affect the activity of RA (DAS28) in patients with RA and suffering from UTI. This means that the bacterial infection of the urinary tract did not affect the DAS28 value of patients under the stress of different RA medicines.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Ethical Committee of the Ministry of Health, Baghdad, Iraq (No 79, 2022).

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Author affiliation

1. *Al-Kindi Hospital, Ministry of Health, Baghdad, Iraq.*

ORCID IDs:

1. Rusul H. Ahmed: https://orcid.org/0009-0000-3251-7539