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Tocilizumab and IL-6 Signaling in Rheumatoid Arthritis: Clinical Implications for Infection Detection and CRP Limitations (Narrative Review with a Retrospective Case Series)

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ABSTRACT

Objective: To consolidate current knowledge regarding the diagnostic challenges associated with interleukin-6 (IL-6) inhibition, to describe reported clinical infections occurring during tocilizumab (TCZ) therapy, and to evaluate its therapeutic efficacy and safety profile.

Methods: A retrospective case series was conducted at Tel Aviv Medical Center (Helsinki Committee approved). Nine patients with rheumatoid arthritis receiving tocilizumab who developed confirmed infections between 2022 and 2025 were included. Data collected included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and clinical outcomes. Infection was confirmed based on clinical findings, laboratory investigations, and imaging studies.

Results: Nine hospital admissions that met the inclusion criteria were identified. Seven patients were receiving tocilizumab for rheumatoid arthritis, while two were treated for giant cell arteritis. TCZ was administered intravenously once monthly in seven patients and subcutaneously once weekly in two patients.

Conclusion: Tocilizumab is effective in rheumatoid arthritis but may mask inflammatory responses by suppressing CRP levels. Clinicians should not rely solely on CRP for infection detection and should incorporate clinical assessment and alternative biomarkers to avoid delayed diagnosis.

Keywords: "tocilizumab", "IL-6 blockade", "CRP suppression", "rheumatoid arthritis", and "infection"

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disorder characterized by synovial inflammation, leading to cartilage destruction, bone erosion, and irreversible joint damage. It affects approximately 0.5–1% of the global population and remains a major cause of disability and reduced quality of life worldwide.

The pathophysiology of RA is complex and involves an interplay between genetic susceptibility and environmental factors. The strongest genetic association lies within the human leukocyte antigen (HLA) class II region, particularly shared epitope alleles, which significantly increase disease risk. Environmental triggers, such as cigarette smoking, microbial infections, and hormonal influences, may initiate disease onset in genetically predisposed individuals.

These interactions lead to a breakdown of immune tolerance and inappropriate activation of both innate and adaptive immune responses. This is characterized by the production of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), along with sustained activation of pro-inflammatory pathways within the synovium [1–2,5–6]

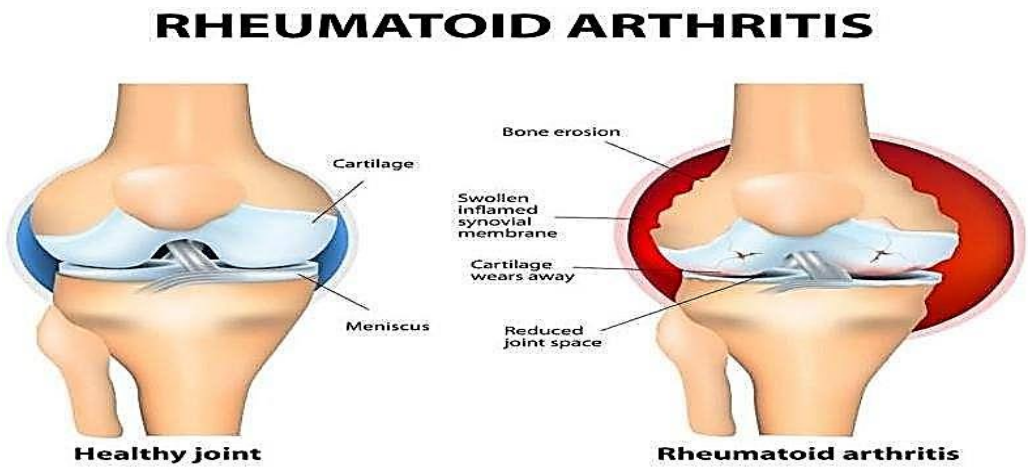

Figure 1: A brief guide to rheumatoid arthritis (effect of rheumatoid arthritis on bones)[41]

1- Epidemiology

RA affects approximately 0.5% of the global population, with more precise estimates from the Global Burden of Disease 2010 study placing the prevalence at ~0.24% (0.23–0.25%) according to ACR criteria. The disease shows a marked female predominance with a female-to-male ratio of about 3:1, and onset most commonly occurs between 35 and 50 years of age, though it may present earlier or later. Geographic variation in prevalence is evident and likely reflects differences in environmental exposures, genetic background, and case ascertainment. Despite advances in treatment that have improved long-term outcomes, RA continues to impose a substantial clinical and economic burden, driven by persistent disability, comorbidities, and the high direct and indirect costs associated with chronic disease management [5, 6].

2-Etiology

RA arises from a complex interplay of genetic susceptibility, epigenetic regulation, and environmental or lifestyle exposures [8,9], rather than a single causative factor. Strong heritability—particularly in seropositive disease—is largely driven by human leukocyte antigen class 2 shared epitope alleles and additional immune [10,11] regulatory variants. Epigenetic alterations, including DNA methylation, histone modifications, and non-coding RNAs, further modulate gene expression and shape individual susceptibility.

Environmental and host-related triggers [12,13]—including smoking, silica exposure, pollutants, and dysbiosis of the gut, oral, and pulmonary microbiota—interact with genetic risk to initiate aberrant mucosal immune activation. Hormonal and reproductive factors also influence disease onset and activity, contributing to sex differences in prevalence. Collectively, these findings highlight RA as a multifactorial autoimmune disease in which genetic risk is amplified or mitigated by epigenetic mechanisms and environmental exposures [14,15].

3-**Pathophysiology**

RA pathogenesis reflects a multilayered interplay between innate and adaptive immune mechanisms, involving neutrophils, macrophages, T and B lymphocytes, and their mediators (16,17) , A prolonged preclinical phase precedes clinical onset, during which autoantibodies such as anti-citrullinated protein antibodies (ACPA) emerge and immunological tolerance is progressively lost. Following disease initiation, synovial inflammation and pannus formation are driven by synovial hyperplasia, angiogenesis, and infiltration of macrophages, dendritic cells, fibroblast-like synoviocytes, and lymphocytes.

These cells secrete proinflammatory cytokines and chemokines, together with matrix metalloproteinases, resulting in cartilage destruction and progressive bone erosion (18,19). Dysregulation of the stromal-immune axis, increased receptor activator of nuclear factor kappa B ligand (RANKL) expression, and activation of osteoclast-mediated bone resorption further consolidate chronicity. Immune complexes involving anti-citrullinated protein antibodies (ACPA) and interleukin-17 (IL-17) enhance complement activation and Fc-receptor–mediated inflammation, while epigenetic alterations, interleukin-6/interleukin-6 receptor (IL-6/IL-6R) signaling, and metabolic reprogramming amplify systemic features and maintain disease persistence.

Emerging evidence highlights contributions from receptor activator of nuclear factor kappa B (RANK)/receptor activator of nuclear factor kappa B ligand (RANKL)/osteoprotegerin (OPG) pathway changes, microRNAs, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway dysregulation, and stromal–immune remodeling, including the formation of ectopic lymphoid aggregates, which reinforce a self-sustaining proinflammatory microenvironment (20,21). Collectively, these findings underscore RA as a dynamic, self-propagating immunoinflammatory disease maintained by reciprocal feedback loops across immune, stromal, and metabolic networks (Figure 2).

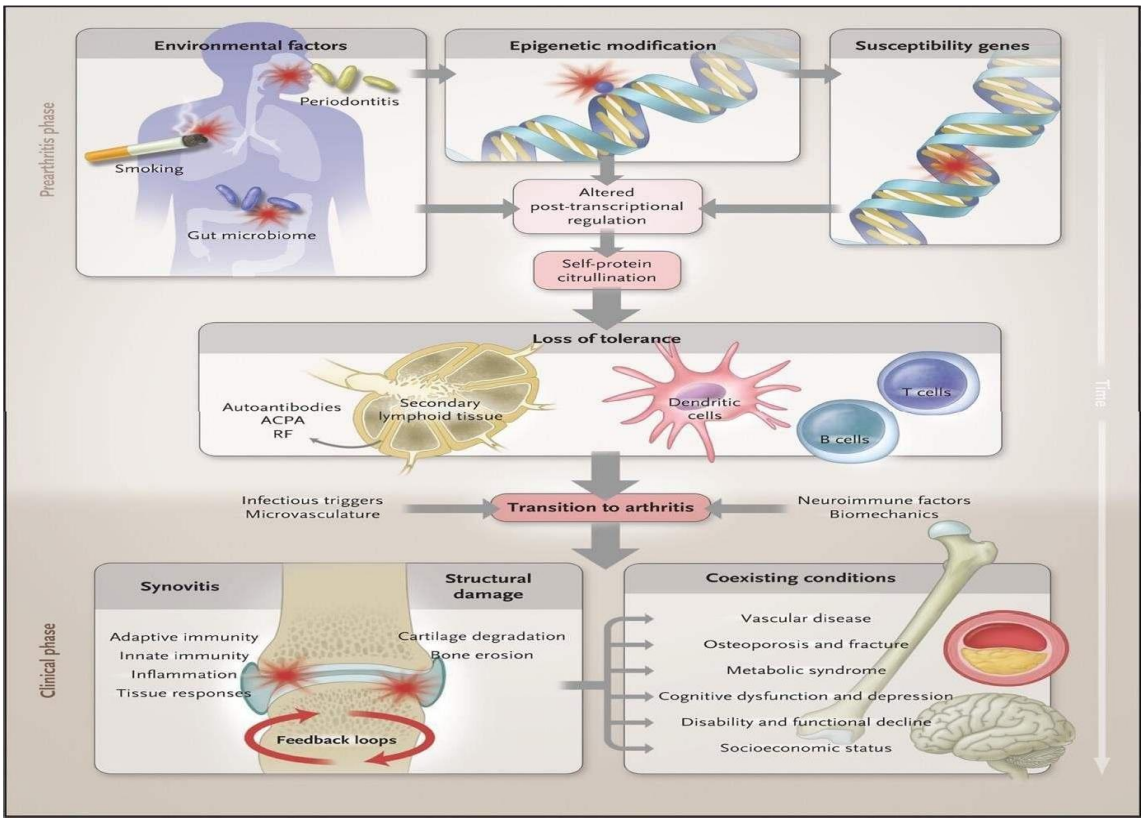

Figure 2: the pathogenesis of rheumatoid arthritis [42]

4-Sign & symptoms

presents with a heterogeneous but characteristically symmetrical polyarticular pattern, most prominently affecting wrist joints, with larger joints such as the knees, shoulders, and ankles becoming involved as the disease progresses (22, 23). Early symptoms typically include fatigue, reduced grip strength, joint pain, warmth, and prolonged morning stiffness exceeding 30 minutes (Figure 3). Persistent inflammation leads to progressive structural deformities, including ulnar deviation, swan-neck and boutonnière deformities (Figure 4), and joint subluxation, which contribute to functional impairment and difficulty performing fine motor tasks (26, 27). Extra-articular features are common and may include constitutional symptoms—such as malaise, low-grade fever, weight loss, and anorexia—as well as rheumatoid nodules on extensor surfaces (24, 25). Systemic involvement can affect multiple organs, manifesting as interstitial lung disease, pleuritis, pericarditis, neuropathy, secondary Sjogren's syndrome, ocular inflammation (scleritis, episcleritis), and rheumatoid osteoporosis. Disease activity often follows a relapsing–remitting course, with flares and periods of partial remission influenced by inflammation, chronicity, and response to therapy (26, 27). Collectively, these clinical and extra-articular manifestations underscore RA as a systemic autoimmune disorder with substantial musculoskeletal and multisystem burden.

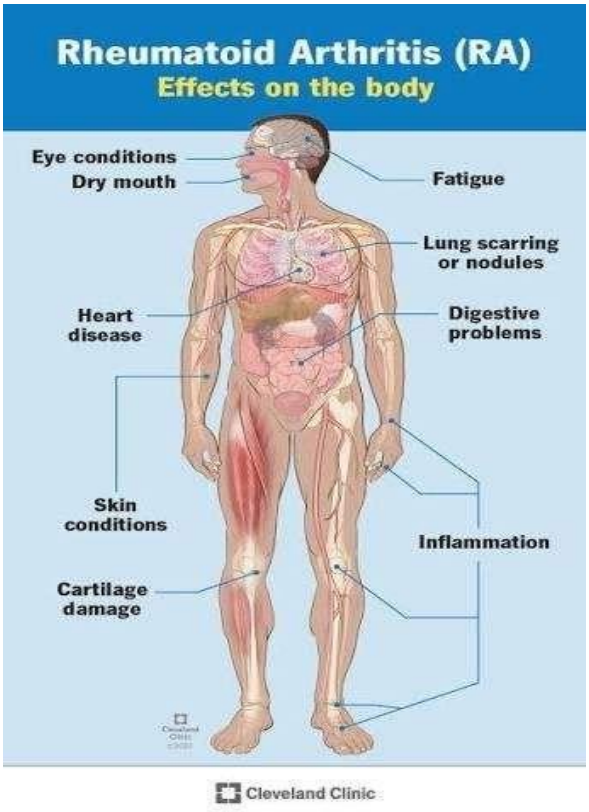

Figure 3: Sign&symptoms of rheumatoid [43] rheumatoid arthritis) [43]

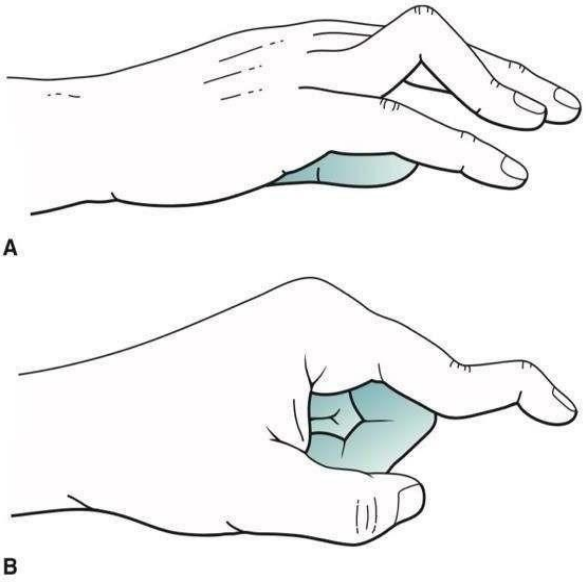

Figure 4:swan-neck and boutonnière (symptoms due to

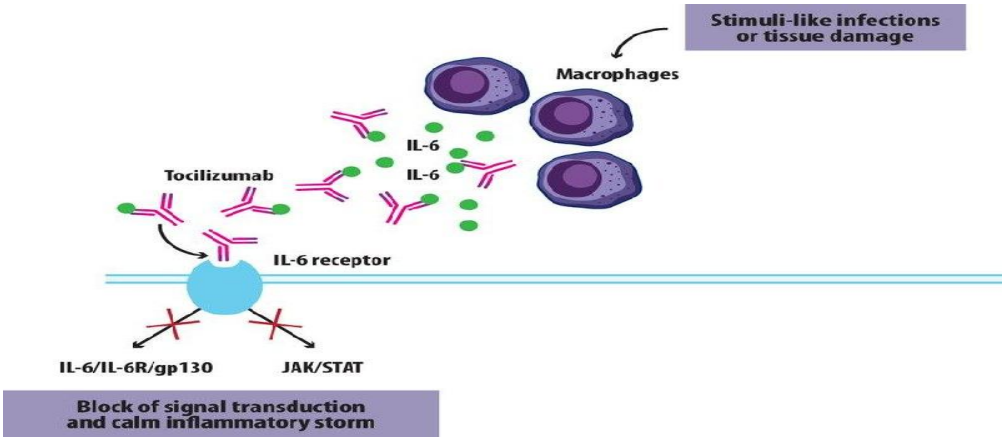

Figure 5: Mechanism of action of tocilizumab (effect of tocilizumab in the body) [44]

5-Diagnosis and imaging

ACR/EULAR Classification Criteria (score-based): includes joint involvement, serology (rheumatoid factor RF), anti-cyclic citrullinated peptide antibodies/anti-citrullinated protein antibodies (anti-CCP/ACPA), acute phase reactants (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and symptom duration. A total of ≥6 points classifies

RA;1987 ACR criteria are less sensitive in early disease [28-29].

6-key Laboratory Tests

The diagnosis and assessment of RA rely on a combination of acute-phase reactants, autoantibody testing, imaging modalities, and emerging molecular biomarkers. Elevated CRP and ESR remain widely used as indicators of systemic inflammation and correlate with disease activity, often declining rapidly with effective therapy [30, 31]. Autoantibodies—including RF and anti-CCP, the latter demonstrating approximately 95% specificity—provide valuable diagnostic and prognostic information, while additional markers such as anti-carbamylated protein (anti-CarP) antibodies may support evaluation, particularly in seronegative cases. Complement levels, immunoglobulin profiles, complete blood counts, liver and renal function tests, and metabolic panels are routinely employed to assist differential diagnosis and establish treatment baselines [32, 33]. Imaging plays a critical role: radiographs detect joint space narrowing, erosions, and periarticular osteopenia; ultrasound, particularly with Doppler, facilitates early detection of synovitis and guides monitoring; and MRI offers high sensitivity for identifying bone marrow edema, synovitis, and erosive changes at early stages [36, 37]. Emerging research tools—including cytokine profiling, matrix metalloproteinase assays, RNA sequencing, and molecular signatures such as IL-6 pathways, genetic variants, and epigenetic markers—show promise for precision medicine approaches and individualized therapy selection [34, 35]. Collectively, these diagnostic strategies form an integrated framework for accurate classification, disease monitoring, and early therapeutic intervention in RA.

7-Pharmacologic effect of IL 6 inhibitor

In rheumatoid arthritis The incomparable effect of clazakizumab for biologicals, like sarilumab, is the selectivity for the interleukin-6 receptor, which directly sends the same signals of interleukin-6 inhibition and represses disease pathogens.

Incomparable inhibitor drugs do not all have the classical actions; blocking of biological inhibitors of the receptor and sarilumab occurs in RA ways and sarilumab-distinguishable ways [1, 2, 3-7]. The biological drug (tocilizumab) is a humanized monoclonal antibody, direct signaling, and the other monoclonal antibody that binds to several locations on IL-6, halting the classical process. Olamkicept [1,2,3-7] follows a different mechanism and is less complex than other biological drugs, such as clazakizumab, which has a classical structure [1-3, 4-7, 8].

TREATMENT

The goals of treatment in RA are to (a) reduce or eliminate pain, (b) reduce disease activity to the lowest possible level, ideally remission, as soon as possible, (c) protect articular structures and function, (d) control systemic complications, and (e) improve/maintain quality of life [13,14-19].

BACKGROUND

a- Tocilizumab (IL-6R) antagonist

EFFECT:- Tocilizumab is the approved treatment for interleukin inhibition as a membrane-bound therapy for patients with rheumatoid arthritis; it is a humanized recombinant IgG1 monoclonal antibody that attaches to inflammatory and combined interleukin-6 receptors (Figure 5), blocking their action and decreasing the initial effect cascade, which was established in 2008 and has shown an adequate response [1, 2-7].

HOW IT WORKS:- Tocilizumab (TCZ) is a human antibody that targets the interleukin 6 receptor (IL-6R). It is approved for treating giant arthritis (RA) in patients who do not respond comfortably to, or cannot tolerate, disease-modifying antirheumatic drugs (DMARDs) [3, 7]. Recently, it has also been approved for treating a condition known as giant cell arteritis. TCZ is a fully humanized monoclonal antibody that targets interleukin-6 to help reduce inflammation by limiting the interleukin-6 of IL-6 on immune cells such as neutrophils, T cells, B cells, and monocytes. Overall, TCZ is comfortably tolerated, but it has caused some side effects, including higher liver enzyme levels, increased cholesterol, and osteoclasts. human risk of infections [7-16-18].

Interleukin-6 is a synthesized cytokine (pro-inflammatory) in the hepatic stages of many. It stimulates the initial acute phase reaction and levels of the main protein named through inflammation. It plays a role in the response to inflammation caused by pneumococci and other diseases, including autoimmune diseases. There is a synthesized pro-inflammatory relationship between the rising levels of the pneumococci, being inflamed, and the mediators of the gene with interleukin-6 during the initial stimulation of C- reactive protein. These proteins are named according to the 100-fold effect of their proteoglycan-c on the inflammation. This protein plays a major role in inflammatory diseases. It is essential during defense against bacteria and microbes. C-reactive protein, implicated in syntheses through the initial stage, is able to bind across difficulty in inflammation inducers [5-11].

It is believed that during sepsis, the immune response involving C-reactive Protein represents a classic reaction to the infectious agent, which plays a crucial role in the CRP interaction cascade pathway, including phosphocholine and its related processes. Much research has demonstrated that most are vulnerable to inflammation. The reaction-causing agent of many bacteria, like S. pneumoniae and other types of bacteria, and its causes of influenza, C-reactive protein, and comfortably meta-analyzed sepsis, and their rate rises through the pathogen infection (bacteria) by a proverbial show in patients with their immune system suppressed; they do not appear to have the interaction sign and symptoms, such as temperature elevation, and the rise in the rate increase commonly appears. The use of such an analysis, like meta-analysis, on a useful number of severely ill patients who have their immune systems suppressed shows a marker or an approach for inflammation [1, 2, 4, 16].

TCZ treatment is answerable as a binding of interleukin-6 to the membrane from affecting interleukin-6 receptors, TCZ its effects, and the fungal effect on the C-reactive protein rate, and thereby interleukin-6 from the animal showed an increased CRP. and fungous show sensitivity to infections. A lot of analysis of former no danger from Tocilizumab treatment on patients with rheumatoid arthritis as a real-world experience focuses on impaired level of integrated inflammation up to a hundred for the eight milligrams/kilogram of population. It appears and shows that the C-Reactive Protein rate and, for a short time after the tocilizumab regimen, have otherwise been noticed in such an infectious person with a not-high temperature, as well as the outcome of the dangerous 8 mg/kg integrated result of the former C-reactive protein [1-7-18].

b- ***Efficacy***

Tocilizumab has shown strong effectiveness in treating early, progressive rheumatic arthritis (RA), both drugs alone or combined with methotrexate (MTX). Studies have found that the combination of patients alone and MTX works better than adalimumab. For example, after 24 weeks of those using tocilizumab, 45% reached remission, compared to only 15% of those using MTX. Tocilizumab worked comfortably as a single treatment, while 45% of those using methotrexate reached remission by week 24 [1, 2, 3]. Another study found that tocilizumab alone was not as operational in reducing RA symptoms as MTX alone was in reducing them, and those who could not tolerate MTX alone were reaching remission. for whom MTX alone [1-3-31].

Because of this strong alternative, the European Alliance of Conventional Therapies for Patients (EULAR) recommends IL-6 receptor blockers like MTX as a preferred biological option for patients who cannot take MTX. The effectiveness of conventional treatment, whether used with MTX or combinations on its own, suggests that it could be a preferred alternative to traditionalistic first- line treatments like MTX or combinations of these DMARDs in early RA [13, 14].

b- *Safety*

is a monumental part of the infection combination treatment. Tocilizumab is monumental. comfortably tolerated, but it is harder to take the risk, which is the risk of diverticulitis and, in rare cases, gastrointestinal perforation. A meta-analysis of infection trials showed that using tocilizumab with methotrexate (MTX) in RA patients slightly increased the risk of infection effects compared to methotrexate alone (odds ratio 1.30; 95% CI: 1.26–1.86). This level of selection is similar to what was observed with the previous bioUlogical treatments, The identical analysis found a higher chance of early infections and more than one therapy in contrast to self-detection (odds ratio 1.53; 95% CI: 1.07–1.58). Because tocilizumab lowers C-reactive protein (CRP) levels, it makes it harder to detect MTX infections early, so close monitoring is monumental [1-7-16-18-29].

Former imaginable side effects include elevated liver enzymes, higher cholesterol levels, and some colorless blood cell counts (neutropenia). However, studies have not found an increased risk of cancer or heart problems with semipermanent tocilizumab use. On the positive side, tocilizumab use. However, there is a significantly reduced risk of causing tuberculosis reactivation, and weakened post-marketing data even suggest that tocilizumab might lower cardiovascular disease risk over time [6-12-32-34].

c- Role in clinical practice

IL-6 inhibitors can fail and are operationally used as second-line biologic treatments for many with dangerous arthritis (RA) who do not work with enough inhibitors. This approach is partially receivable to tumor necrosis factor (TNF) considerations and past treatment outcomes.

Although TNF inhibitors (TNFis) are operational for many patients who have RA, about 30–40% stop using them because they do not respond comfortably to them or they cause side effects. When TNF inhibitors are switched to TNF distinguishable with a useful mechanism such as second-line IL-6 inhibitors, it is an operational next step. Targeting IL-6 inhibitors is a useful disjunctive for many who do not respond to inhibitors as a second line, which can improve overall treatment outcomes [1, 2-13, 14, 15].

However, responses to treatment. inhibitors can also differ between individuals because of differences in the levels and reflect unhealthy processes of differences in IL-6 activity. Underlying IL-6 can also change throughout the blood, which may affect how patients respond to IL-6. Although measuring IL-6 levels is not yet a routine practice, C-reactive protein is not tested, and interleukin- 6 levels are not tracked over time. Monitoring CRP levels, along with other unhealthy markers, may affect further personalized treatment strategies for RA in IL-6 blood [4.5-25].

d- Benefits

One of the primary overall benefits that appears in rheumatoid arthritis (RA) is the quick improvement of anemia with therapy. disease. Around 16% of patients diagnosed with rheumatoid arthritis (RA) also have anemia, and 60% of these patients will experience anemia at some point in their lives [30-37].

LOWRING CRP:Anemia is a serious condition that can lead to a faster progression of rheumatoid arthritis (RA). IL-6 inhibition works by reducing IL- 6's effect on iron metabolism, lowering hepcidin levels, and combating anemia. For example, patients treated for rheumatoid arthritis (RA) showed a moderate increase in hemoglobin levels, measured in g/dL, after 12 weeks of IL-6 inhibition, and further research on this topic has been conducted multiple times in the RA quick group [4-25-36] ·Conditions like congestive heart disease and insulin compared to prevailing in RA. Studies show that RA patients have double the hazard of chronic heart failure and improve their chances of diabetes mellitus compared to people without RA [8-9-14]. IL-6 inhibition helps reduce inflammation and cardiovascular blood sugar control by lowering glycosylated hemoglobin and thrombosis. resistance, which lowers the risk of heart failure. For instance, intravenous tocilizumab may reduce insulin resistance or cardiovascular resistance in nondiabetic RA patients, suggesting it could help prevent metabolic syndrome and lower the risk of cardiovascular events. In such a study comparing patients who have rheumatoid arthritis, those treated with TCZ had relief compared to those who did not receive biologic therapy; those treated with people reduced the lower help heart molecule linked to higher cardiovascular risk. Lowering these levels and reducing the incidence of lipoprotein(a) and improvement [6-10-12-34, 35].

However, treatment with IL-6 inhibition. appear to improve total cholesterol, triglycerides, and 44% ("good cholesterol"). Interestingly, the overall cardiovascular effects of TNF inhibitors can be similar to those of TNF inhibitors. RA also improves outstanding gushiness and reduces health impacts. About 22% of osteoporotic people use antidepressants, 19% report anxiety, and those with high- density lipoprotein experience fatigue. These symptoms can also improve with IL-6 inhibitors; former benefits include lowering the overall IL-6 fractions (which are about double as shared in RA) and improving bone loss. muscle strength, and 44% markers of osteoporotic density [20, 21-24, 35].

MATERIAL AND METHOD

This study was approved by the institutional ethical committee of [Tel Aviv Medical Center]. Patient confidentiality was maintained in accordance with the Declaration of Helsinki

narrative literature review was conducted using PubMed, Google Scholar, and Scopus databases. The following keywords were used: "tocilizumab", "IL-6 blockade", "CRP suppression", "rheumatoid arthritis", and "infection". Articles published between 2005 and 2025 were included. Only English-language human studies were considered

this retrospective case series was conducted at Tel Aviv Medical Center (Helsinki committee)
We included 9 patients diagnosed with rheumatoid arthritis who were receiving tocilizumab and developed confirmed infections between [2022–2025]. Data collected included CRP, ESR, WBC count, and clinical outcomes. Infection was confirmed based on clinical findings, laboratory tests, and imaging

- Case 1: A 59-year-old male with seronegative rheumatoid arthritis on long-term tocilizumab developed Whipple disease endocarditis, presenting with embolic cerebral lesions. Notwithstanding the acute infection, CRP levels were within the normal range. The diagnosis was validated through PCR analysis of the excised valve, and the patient recuperated with ceftriaxone, subsequently followed by TMP-SMX.

- Case 2: A 73-year-old woman in remission from rheumatoid arthritis, undergoing treatment with tocilizumab for nine years, came with pneumonia in the right lower lobe. She exhibited normal CRP levels and moderate leukocytosis. She had rapid improvement with ceftriaxone.

- Case 3: A 55-year-old female patient undergoing treatment with TCZ for rheumatoid arthritis presented with left lower lobe pneumonia, characterized by fever, leukocytosis, hemoptysis, and pleuritic discomfort. The initial rise of CRP was negligible, increasing solely after hospitalization and subsequently decreasing in response to treatment.

- Case 4: A 67-year-old male with rheumatoid arthritis and a history of lymphoma developed a cervical paraspinal abscess due to Streptococcus pneumoniae while receiving therapy with TCZ, exhibiting slight leukocytosis and a modest elevation in CRP levels. Antibiotics and surgical drainage worked.
- Case 5: An 88-year-old female patient, recently initiated on TCZ, presented with cellulitis and an infected hematoma. Despite the presence of a clear infection, her CRP levels were just marginally increased. She recovered following the use of intravenous cefazolin.
- Case 6: An 86-year-old woman with giant cell arteritis on tocilizumab developed a cervical abscess, presenting as purulent vaginal discharge. CRP levels were either normal or marginally elevated, and symptoms diminished after hysterectomy and antibacterial therapy.
- Case 7: A 64-year-old male with giant cell arteritis exhibited symptoms akin to bacterial meningitis immediately after the commencement of tocilizumab, characterized by normal C-reactive protein levels and purulent cerebrospinal fluid. Despite the negative cultures, he responded favorably to broad-spectrum antibiotics.
- Case 8: A 62-year-old woman who had been taking tocilizumab (TCZ) for seven years came in with a pelvic abscess and perforated diverticulitis. The CRP level was normal despite the presence of an acute intra-abdominal infection in the patient. The surgical procedure and rehabilitation progressed without complications.
- Case 9: A 76-year-old female patient, post-lung cancer surgery and on treatment with TCZ, developed bilateral pneumonia and respiratory failure. Initially, the CRP level was moderate (8 mg/L), but it escalated rapidly as the patient's condition deteriorated. She improved following the administration of antibiotics and the use of a ventilator.

RESULTS

Nine hospital admissions that met the inclusion criteria were identified. Seven patients were receiving tocilizumab (TCZ) for rheumatoid arthritis, while two were treated for giant cell arteritis. TCZ was given intravenously once monthly in seven patients and subcutaneously once weekly in two patients. The main causes of hospitalization were pneumonia (n = 3), osteomyelitis (n = 1), cellulitis (n = 1), Whipple disease–associated endocarditis (n = 1), cervical uterine abscess (n = 1), meningitis (n = 1), and perforated diverticulitis with an intra-abdominal abscess (n = 1). The mean C-reactive protein (CRP) level at admission was 4.75 mg/L (range: 0.03–16 mg/L). CRP was normal in four cases, mildly elevated in four cases (less than twice the upper limit), and markedly elevated in one case (16 mg/L).

Table 1 : Results and outcome after tocilizumab therapy (9 patient and their clinical outcome after taking tocilizumab) RA, rheumatoid arthritis; GCA, giant cell arteritis; TCZ, tocilizumab; CRP, C-reactive protein; RLL, right lower lobe; LLL, left lower lobe; Tx, treatment

CASE	1	2	3	4	5	6	7	8	9
Diagnosis	RA	RA	RA	RA	RA	GCA	GCA	RA	RA
Age	59	73	55	67	88	86	64	62	16
Gender	M	F	F	M	F	F	M	F	F
Duration TCZ of treatment	4 years	9 years	3 months	3 years	3 months	2 months	3 weeks	7 years	2 years
Infection diagnosed	Whipple disease endocarditis	RLL lobar pneumonia	LLL pneumonia	Streptococcuspneumonia skin abcess	Left leg Cellulitis	Abcess of cervix uteri	Meningitis	perforated diverticulitis with intra-abdominal abscess	Bilateral pneumonia
CRP on admission(mg/L)	0.97	0.03	6.8	16	7.9	2.2	0.03	0.8	8
Duration of hospitalisation,days	>1 month	4	5	7	3	5	10	7	14
Resolution of infection (all improved)	After valve replacement and prolonged antibiotic Tx	Rapid	Rapid	Gradual	Gradual	after hysterectomy	Gradual	After colostomy and antibiotic Tx	Gradual

RA, rheumatoid arthritis; GCA, giant cell arteritis; TCZ, tocilizumab; CRP, C-reactive protein; RLL, right lower lobe; LLL, left lower lobe; Tx, treatment.

DISCUSSION

- This study demonstrates that Tocilizumab profoundly suppresses the acute-phase response, particularly by inhibiting C-reactive protein (CRP) elevation and fever even in the presence of severe bacterial infections. Notably, more than half of patients exhibited normal or only minimally elevated CRP levels at the time of clinical assessment despite serious conditions such as meningitis, necrotizing fasciitis, osteomyelitis, septic arthritis, and disseminated bacterial infections. This blunted inflammatory response represents a critical diagnostic limitation, as it may mask infection and delay recognition, thereby increasing the risk of adverse out

- Biological Mechanism:The underlying mechanism is directly related to the inhibition of Interleukin-6 signaling. Under normal physiological conditions, IL-6 plays a central role in stimulating hepatocytes to produce acute-phase reactants, including CRP, fibrinogen, and serum amyloid A. By blocking the IL-6 receptor, tocilizumab interrupts this signaling cascade, leading to reduced hepatic synthesis of CRP despite ongoing inflammatory or infectious processes. Consequently, traditional biomarkers such as CRP become unreliable indicators of infection in patients receiving IL-6 inhibitors.

- comparison with Literature:These findings are consistent with previously published studies and international guidelines, which have highlighted the limitations of CRP monitoring in patients treated with IL-6 inhibitors. Multiple observational studies have reported suppressed CRP responses during severe infections in patients on tocilizumab therapy, emphasizing that CRP levels do not accurately reflect disease severity in this population. Furthermore, clinical guidelines for the management of rheumatoid arthritis and biologic therapies caution clinicians about the potential masking of infection and stress the importance of careful clinical evaluation beyond laboratory markers.

- Clinical Recommendations :Given these challenges, reliance on CRP alone is strongly discouraged in patients receiving tocilizumab. Instead, clinicians should adopt a multimodal approach to infection assessment. Alternative biomarkers such as Procalcitonin (PCT) and the Neutrophil-to-Lymphocyte Ratio (NLR) may provide more reliable indicators of bacterial infection. Additionally, close attention to clinical symptoms-often the earliest and most sensitive indicators-along with appropriate imaging studies and microbiological cultures, is essential. In cases of suspected infection, early initiation of empirical antibiotic therapy should be considered to prevent progression and improve patient outcomes. These strategies highlight the need for heightened clinical vigilance and individualized assessment in this high-risk population.

CONCLUSION

Tocilizumab is effective in rheumatoid arthritis but may mask inflammatory responses by suppressing CRP levels. Clinicians should not rely solely on CRP for infection detection and must incorporate clinical evaluation and alternative biomarkers to avoid delayed diagnosiss.

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CONFLICTS OF INTEREST

The authors did not disclose any conflicts of interest

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توسيليزوماب وإشارات الإنترلوكين-6 في التهاب المفاصل الروماتويدي: الانعكاسات السريرية على تشخيص العدوى وحدود البروتين المتفاعل سي (مراجعة سردية مع سلسلة حالات استعادية)

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الخلاصة

الهدف: يهدف هذا العمل إلى تجميع المعرفة الحالية المتعلقة بالتحديات التشخيصية المرتبطة بتثبيط الإنترلوكين-6(IL-6) ، ووصف حالات العدوى السريرية المُبلّغ عنها أثناء العلاج بالتوسيليزوماب(TCZ) ، بالإضافة إلى تقييم فعاليته العلاجية وملفه من حيث السلامة.

المنهجية: أُجريت سلسلة حالات استعادية (Retrospective case series) في مركز تل أبيب الطبي بعد الحصول على موافقة لجنة هلسنكي. شملت الدراسة تسعة مرضى مصابين بالتهاب المفاصل الروماتويدي ويتلقون علاج التوسيليزوماب، وقد طوّروا حالات عدوى مؤكدة خلال الفترة من 2022 إلى 2025. تم جمع البيانات المتعلقة بمستويات البروتين المتفاعل(CRP) C ، ومعدل ترسيب كريات الدم الحمراء(ESR) ، وعدد كريات الدم البيضاء (WBC)، بالإضافة إلى النتائج السريرية. وتم تأكيد العدوى استنادًا إلى التقييم السريري والفحوصات المخبرية والدراسات التصويرية.

النتائج: تم تحديد تسع حالات دخول إلى المستشفى استوفت معايير الاشتمال. كان سبعة مرضى يتلقون التوسيليزوماب لعلاج التهاب المفاصل الروماتويدي، في حين تم علاج مريضين بسبب التهاب الشرايين ذو الخلايا العملاقة. أُعطي التوسيليزوماب عن طريق التسريب الوريدي مرة واحدة شهريًا لدى سبعة مرضى، بينما أُعطي تحت الجلد مرة واحدة أسبوعيًا لدى مريضين.

الاستنتاج: يُعد التوسيليزوماب علاجًا فعالًا لالتهاب المفاصل الروماتويدي، إلا أنه قد يُخفي الاستجابة الالتهابية من خلال تثبيط مستويات .CRP لذلك، ينبغي على الأطباء عدم الاعتماد على CRP وحده في تشخيص العدوى، بل يجب دمج التقييم السريري واستخدام مؤشرات حيوية بديلة لتجنب تأخر التشخيص.

الكلمات المفتاحية: توسيليزوماب، تثبيط IL-6، تثبيط CRP، التهاب المفاصل الروماتويدي، العدوى