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Review Article

TNF- α inhibitors and post-operative surgical site infections in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and systemic complications. Its diagnosis and progression are monitored via biomarkers such as rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ACPA), and others. However, their predictive utility varies among patients. While some patients respond well to methotrexate, others have better outcomes with drugs like rituximab and tocilizumab. Research is focusing on biomarkers for structural damage, including bone erosion and cartilage destruction, linked to genetic variants like HLA-DRB1, CD40, and IL2RA. Inflammatory and bone/cartilage turnover markers are also under study. Synovial biopsy reveals insights into RA pathophysiology, with synovial heterogeneity associated with therapeutic responses. Blood transcriptome analysis could provide potential biomarkers, such as the Interferon gene signature and IgJ, which reflect disease stage and treatment response. Anti-TNF-alpha treatments have improved RA outcomes but should be used cautiously in heart disease patients. Uncertainty persists about the risk of surgical site infections in patients on TNF inhibitors and the potential increased risk of serious infections with anti-TNF therapy. Vaccination is recommended before anti-TNF treatment. Standardized methodologies and more research are needed to establish effective clinical guidelines.

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1. Introduction

Rheumatoid arthritis is a chronic autoimmune systemic inflammatory disease with articular and extra-articular manifestations.¹ Rheumatoid arthritis typically presents with insidious onset of symmetrical polyarthritis of hands, wrists, and feet over a period of weeks to months. The disease causes progressive cartilage and joint destruction and bony erosions. Systemic manifestations include fatigue, weight loss, and fever. Extra-articular complications occur primarily in long-standing, untreated disease and include hematologic, ophthalmologic, vascular, pulmonary, cardiac, renal, and neurologic disease.^{1,2} Specific joint involvement,

duration of symptoms, and presence or absence of abnormal laboratory test results (rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies plus erythrocyte sedimentation rate and/or C-reactive protein) are factors used in a scoring system to classify a patient as likely to have rheumatoid arthritis for purposes of treatment initiation.³ Early, aggressive treatment with disease-modifying antirheumatic drugs (traditional or biologic) is important to prevent deformity and disability. Remission is attained by up to half of all patients with early disease treated with methotrexate and a biologic disease-modifying antirheumatic drug. Patients with rheumatoid arthritis are at risk of accelerated cardiovascular disease and risk factors should be aggressively managed.^{3,4} Rheumatoid factor is

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present in some people who never develop the disease; it should not be used as the sole diagnostic criterion. Glucocorticoids are used as bridge therapy before a new disease-modifying antirheumatic drug is fully effective, but dosages beyond 10-mg prednisone per day are rarely needed; use for the shortest possible duration.⁵

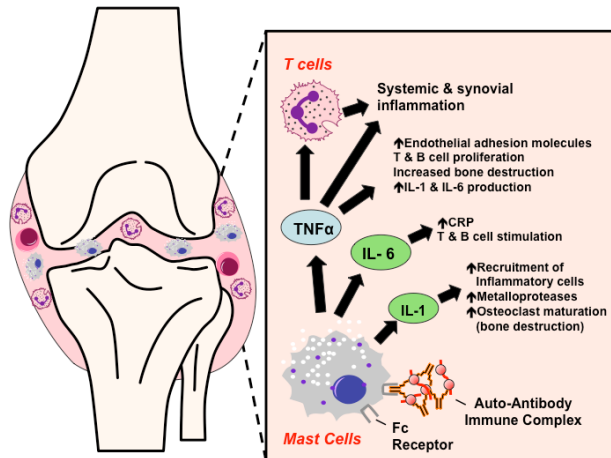


Fig. 1:

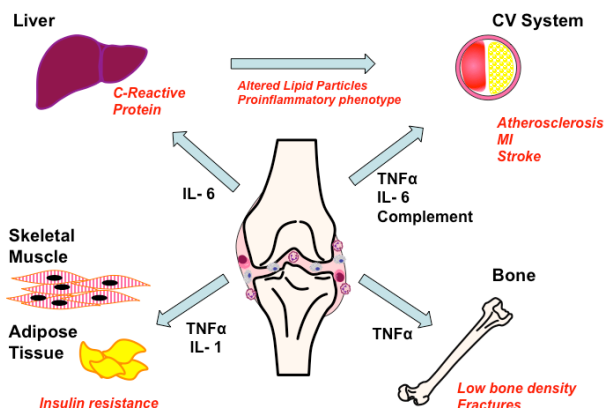


Fig. 2:

2. Markers of RA

Efforts have been made to identify patients at risk of developing clinical disease as well as defining clinical features and biomarkers of patients who are most at risk of bone erosion and cartilage damage in the progression of rheumatoid arthritis. These biomarkers are widely used in clinical practise because they are supported by numerous clinical studies and have well-validated assays. Early disease detection and treatment are linked to less structural damage and a higher chance of clinical

remission being achieved.⁶ The pre-clinical state of disease, or pre-RA, where disease processes are already active even though the patient has not yet met formal RA clinical diagnostic criteria, is a major focus of research efforts.⁷ Monitoring disease activity in the context of drug treatment and understanding disease heterogeneity by identifying biomarkers that predict patient response to targeted therapies have both been pursued simultaneously.

3. Autoantibodies in Rheumatoid Arthritis

It has long been recognised that the presence of autoantibodies is a key diagnostic sign of RA. Diagnostic and prognostic biomarkers for RA and pre-RA include RF, anti-citrullinated protein antibody ACPA, anti-carbamylated CarP, and anti-mutated citrullinated vimentin (anti-MCV).^{8–11} Antibodies have been studied in relation to treatment outcomes as well as disease risk, diagnosis, and prognosis. ACPA-positive RA patients had a better clinical response to methotrexate than ACPA-negative RA patients. Autoantibodies have been tested to see if they can predict how the body will react to biologic agents with mixed results. The anti-CD20 antibody rituximab and the anti-IL-6 receptor antibody tocilizumab have been shown to improve clinical outcomes in patients with RF positivity, but not with TNF inhibitors or abatacept (CTLA4-Fc, co-stimulation blocking antibody).^{12–14} TNF blockade response can also be predicted by ACPA status, but no consistent effect has been found in multiple studies.

Studies of rituximab and abatacept have yielded more insightful results. Meta-analyses of the pivotal trials of rituximab found that patients with RF and/or ACPA antibody seropositivity had better clinical outcomes, but this benefit was greatest in patients who had previously failed anti-TNF therapies.¹⁵ The presence of autoantibodies has been found to be associated with better clinical outcomes in studies using registries. Abatacept's clinical response has also been found to be greater in patients who are ACPA-positive. The AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) study showed that the greatest decrease in DAS28-CRP scores after treatment with abatacept, but not adalimumab, was observed in patients with the highest ACPA titers.¹⁶ Following treatment with abatacept, a reduction in ACPA levels has been linked to an improvement in clinical outcomes. While rituximab reduces RF and ACPA titers and synovial plasma cells, the reduction in RF/APCA was not correlated with clinical outcomes.

4. Prognostic and Diagnostic Biomarkers of Structural Damage in Rheumatoid Arthritis

In RA, bone erosion and cartilage destruction are common side effects of the inflammatory response. Joint integrity and function are the long-term goals of RA treatment.^{1–3}

Conventional radiography, radiologist-based quantitative assessment of bone erosions, and JSN using validated and health authority-accepted Sharp Score or its modifications, van der Heijde Sharp score (vdH-S), or Genant-Sharp score, are the current gold standard methods for measuring bone and cartilage damage (G-S). As a result, identifying patients with rapidly progressing joint disease is critical for both clinical practise and the design of clinical trials of therapies assessing joint health. Clinical trials spanning several years are typically needed to evaluate the effect of therapies on radiographic progression in the minority of patients (less than 50%) who have worsening Sharp scores over time. The search for biomarkers, such as genes, proteins in the blood and urine, or MRI images that show bone and cartilage turnover, has thus begun. Structural damage biomarkers have been recommended by an OMERACT (Outcome Measures in Rheumatology) task force based on evidence from pre-clinical models, production of the biomarker in joint tissue and correlation with other surrogates of bone or cartilage damage.^{17–19}

5. Genetics

There are only a few reproducible effects of the identified genetic variants on the risk of structural progression because structural damage progression risk is genetically heritable to some extent (50%). RA risk, disease severity, erosive disease, and the presence of ACPA are all linked to the HLA-DRB "shared epitope" (SE).^{20,21} It is possible that the association between SE alleles and radiographic risk may be indirect and partly driven by their association with ACPA status in ACPA-negative patients, as was found in the analysis of ACPA-positive patients. As part of genome-wide association studies or using a candidate gene approach, many other genetic variants have been tested and found to have little or no effect on the risk of joint damage. Inflammation, autoimmunity, bone turnover, and other markers of inflammation and autoimmunity have all been linked in several meta-analyses to radiographic progression.²² The genetic variants associated with radiographic progression in RA is tabulated in Table 1.

6. Protein Biomarkers

Protein biomarkers of radiographic progression risk have received additional attention. Inflammation and bone/cartilage turnover are among the indicators. As previously discussed, autoantibodies (especially ACPA) have been shown to have a strong correlation with progression risk. The acute phase reactants CRP and ESR are associated with a small (less than 20%) risk of progression in patients with inflammatory bowel disease. Many other immune and inflammatory proteins have been shown to be elevated in disease and to be associated

with disease activity metrics, but their clinical utility for assessing disease activity and treatment outcome is unclear. As an example, baseline serum TNF, IL-6, or IL-1 levels have not been predictive of clinical response when receiving therapies targeted against those respective cytokines. The DAS28 score, an imaging-based assessment of joint inflammation and a predictor of radiographic progression, was used to develop a composite biomarker score consisting of 12 serum proteins. Clinical disease activity as measured by the Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and DAS28-CRP had a poor correlation with the biomarkers studied in the AMPLE trial, which was conducted recently. The ability to demonstrate the clinical utility of blood inflammatory proteins beyond the acute phase reactants remains a challenge.

There has also been a lot of work done on biomarkers for bone and cartilage turnover, but none of them have been found to be sensitive, specific, and dynamic enough to be used in clinical decision-making.²³ The progression of joint damage is linked to an increase in serum MMP3, which is linked to the destruction of cartilage and bone. Serum COMP, a chondrocyte marker, is elevated in patients with severe erosive disease and has been linked to joint damage prediction in the context of MMP3.²⁴ This collagen marker, PYD, has been shown to be an excellent predictor of joint destruction in patients with both early and established rheumatoid arthritis.²⁵ There is evidence that the ratio of RANKL (a pro-osteoclast cytokine) to the decoy receptor for RANKL (OPG) may provide an indicator of the balance between the osteoblast and the osteoclast.²⁶ In multiple studies, uCTX-I, a marker of collagen turnover, has been linked to the severity of bone damage. Moreover, this marker predicts severity independent of other known factors, such as autoantibodies and acute phase reactants.²⁷ Serum CTX-I outperforms other cartilage biomarkers, such as COMP and the RANKL/OPG ratio, when it comes to predicting 10-year changes in radiographic scores. Biomarkers like proteolytic products have been described but further research is needed before they can be used in patients.

7. Emerging Rheumatoid Arthritis Biomarkers

7.1. Biomarkers in synovial biopsies

In addition to serum biomarkers, new technologies focusing on the synovial end-organ are being used to assess additional measures of disease activity and treatment response. For the discovery of RA biomarkers, synovial biopsy is a recent addition to the technology arsenal that can aid disease diagnosis, predict prognosis, and provide an early read on therapeutic treatment benefit. The pathophysiology of RA has been elucidated by a variety of techniques, including histological, cellular,

Table 1: List of genetic variants associated with radiographic progression in rheumatoid arthritis

	Gene	Variants	Effect of Minor Allele(s) on Joint Radiographic Severity
Immune genes	HLA-DRB1	SE alleles	Destruction
	CD40	rs4810485	Destruction
	IL2RA	rs2104286	Protection
	IL4R	rs1119132	Destruction
		rs1805011	
		rs1800896	Protection
Bone and cartilage turnover	OPG	rs1485305	Destruction
	DKK1	rs1896368	Destruction
		rs1896367	Protection
		rs1528873	Destruction
	GRZB	rs8192916	Destruction
	MMP3	5A/6A	Destruction
	MMP9	rs11908352	Destruction

immunohistochemical, and transcriptomic analyses.

Studies on the synovial tissues of pre-clinical RA patients with autoantibody positivity suggest that an increase in CD3 + T cell infiltration in the knee synovium may be a predictor of the development of clinical symptoms.²⁸

Early-RA patients' synovium has shown evidence of oligoclonal T cell expansion, the presence of epigenetic changes in fibroblast-like synoviocytes (FLS), and elevated macrophage-associated chemokines indicative of synovial tissue inflammation. A similar pattern of DNA hypermethylation has been found in peripheral blood naive T cells, which could lead to the development of epigenetic biomarkers for synovial pathology in peripheral blood. It is possible to tell RA patients apart from those with non-RA or undifferentiated arthritis by looking for elevated levels of synovial B cell and macrophage markers and increased activity in the Jun-N-terminal kinase (JNK) pathway. Erosive versus non-erosive rheumatoid arthritis patients have been found to have elevated levels of synovial proangiogenic factors and their receptors in their joints. For example, the synovium's lymphocyte aggregates or elevated T cell infiltrates are associated with elevated disease activity such as DAS28 score, the presence of autoantibodies and the elevated expression of cytokines, but do not define a distinct clinical subset of RA. Synovial lymphoid aggregate reduction after anti-TNF therapy was associated with better clinical response, despite the fact that baseline synovial lymphoid aggregates are linked to longer duration of disease and less clinical improvement.^{28–30}

Synovial heterogeneity in cells and molecules has also been linked to therapeutic responses in studies. Rituximab works better in patients with synovial infiltration of B and T cells, as well as the presence of synovial lymphoid aggregates (referred to as the lymphoid phenotype). On the other hand, patients with a significant infiltration of myeloid cells (referred to as the myeloid phenotype) benefit more from anti-TNF therapies. It is known as the "fibroid

phenotype" for a reason: patients who have lower levels of lymphocytic or myeloid infiltrates in their synovial tissue have a poor response to B cell-targeted treatment and exhibit lower levels of acute phase reactants. The importance of synovial macrophages as biomarkers of disease activity and treatment response has been highlighted in numerous studies. Disease activity is linked to the presence of synovial CD68 + sublining macrophages; their decline is strongly linked to a variety of therapies. Many researchers believe that CD68 expression in synovial tissue could serve as a surrogate biomarker for the effectiveness of new anti-rheumatic drugs in patients with RA, especially given the biomarker's replicability across multiple research centres.³⁰

Pharmacodynamic responses to experimental therapies have also been evaluated using synovial tissue analysis. A decrease in synovial tissue levels of phosphorylated forms of STAT1 and STAT3 (JAK substrates) is associated with clinical improvement when given the Janus Kinase inhibitor tofacitinib.³¹ Further insights into the pathogenesis and heterogeneity of patient disease will be gained through the use of new and emerging technologies such as single cell isolation, transcriptomics, and proteomics. If biopsies are made more widely available and potentially adopted into the clinical setting, they could become an important source for biomarkers in clinical practise.

7.2. Blood transcriptomic biomarkers

Transcriptome analysis of whole blood from RA patients has also been undertaken. Because the synovial end-organ pathophysiology is diluted in the blood, weaker signals are generated in these analyses. Some blood transcriptional biomarkers, on the other hand, have been shown in multiple studies to have a consistent effect on clinical outcome. IGS (interferon gene signature) can be detected in preclinical RA and is elevated in 20% to 66% of established RA patients, but variation in IGS depending on disease stage, course, and co-medications complicates the interpretation

of IGS in RA, which is further described in the SLE biomarkers section.³² It has been shown that in patients with established RA, an elevated IGS correlates with a worse clinical response to initial therapy, a better clinical response to anti-TNF or tocilizumab therapy, and an inferior clinical response to rituximab, in patients who have never received treatment. Using IgJ as a transcriptional biomarker surrogate for plasmablast numbers, researchers identified a 25% subgroup of RA patients who had decreased clinical responses to rituximab in multiple clinical trials.³³ To keep track of how a patient is responding to medication, transcriptional profiles may be helpful. Clinical outcomes are associated with gene modules reflecting different immune system ancestries and profiles that consistently decrease in response to anti-TNF therapy.³⁴ They have yet to predict therapeutic outcomes, however, and in general whole blood transcriptional biomarkers have not provided sufficient robustness and reproducibility to be useful for clinical decision making.

8. TNF- α inhibitors in RA

New biologic agents have revolutionised the treatment of rheumatoid arthritis, resulting in better outcomes for patients who were previously resistant to conventional DMARDs. Patients who do not respond to traditional DMARDs are given anti-TNF- α as a first line treatment. Even if a second anti-TNF- α is considered a good option, up to 50% of patients fail to respond to these drugs or experience adverse events that lead to treatment discontinuation. In these cases, the optimal treatment strategy is still up for debate.^{35,36} An Italian rheumatoid arthritis registry's data on patients who switched from a first to a second anti-TNF- α drug shows that patients who stop taking a first anti-TNF drug benefit from switching.³⁷ A second anti-TNF treatment is very likely to be effective in patients who have a higher level of disease activity or who have stopped the first treatment because of its ineffectiveness.³⁷

Active RA, psoriatic arthritis, and ankylosing spondylitis patients benefit from TNF- blockade, which has been shown to be effective in treating these conditions. Both intravenous and subcutaneous injections of monoclonal antibodies can be used to target TNF- α , as well as subcutaneous injections of TNF receptor-fusion protein etanercept. They should be avoided in patients who have a history of heart disease or who have NYHA classes III or IV cardiac failure, and they should be used with caution in patients who have milder forms of congestive heart failure. Carotid IMT progression is accelerated by the combination of systemic inflammation and traditional risk factors in RA. A reduction in cardiovascular events can be achieved by using methotrexate and TNF- α antagonists to slow the progression of the disease.^{38–40}

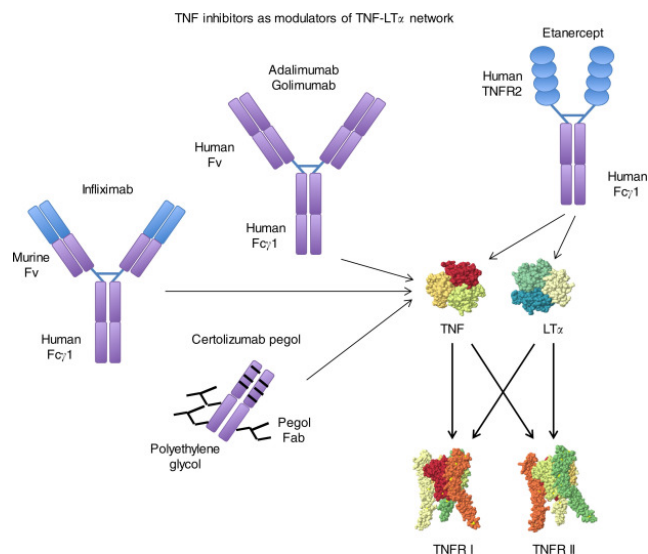


Fig. 3:

8.1. Post-operative surgical site infections in RA

Anti-TNF therapy raises the possibility of SSI risk in patients undergoing orthopaedic surgery who are taking TNF blockade because of its concern for infection. There is a dearth of information available in this area, and the research that has been done thus far has produced mixed results. When comparing surgical site infections (SSI) in elective orthopaedic surgery between two time periods when policy was to discontinue versus continue TNFi perioperatively, it was unable to show that TNFi use was an independent risk factor for SSI.⁴¹ The low number of infections in this study may be a factor in the discrepancy between our findings and this one. When TNFi's were continued after a series of foot and ankle surgeries, there was no increase in infection or wound complications. These findings may have been based on insufficient data in both of these studies. SSIs were included in our study because of the strong link between superficial SSIs and deeper tissue infections, and found that infection rates were higher overall in the TNFi-treated group.⁴²

According to the available literature, a wide range of factors could not be evaluated. However, several studies included these potential covariates in their analysis, including disease activity and RA flares, steroid use, age, smoking and co-morbid conditions such as diabetes. Because TNFis were studied as a group, we don't know the odds of SSI between different types of TNFis. There were no randomised controlled trials, and no studies were conducted with participants unaware of the treatment they were receiving, raising the possibility of a significant selection bias across all studies. A prospective randomised trial requiring a sample size of more than 50 000 patients would be required to answer this question definitively.

given the standardised infection ratio for THA at one institution (0.46). For this analysis, retrospective studies, cohort studies, and case control studies were used.^{43,44}

These findings support the practise of not administering TNFi to patients before orthopaedic surgery, but they must be viewed in the context of possible limitations. According to the CDC, six studies identified SSI as the cause of the symptoms. Definitions were rigorous, even if there was some inconsistency in how they were used, which may have led to an undercount of infections. Even after we divided the studies into two smaller subgroups according to whether they met the ACR's criteria for diagnosing RA or the CDC's for diagnosing SSI, pre-operative exposure to TNFi remained a significant risk factor for infection.

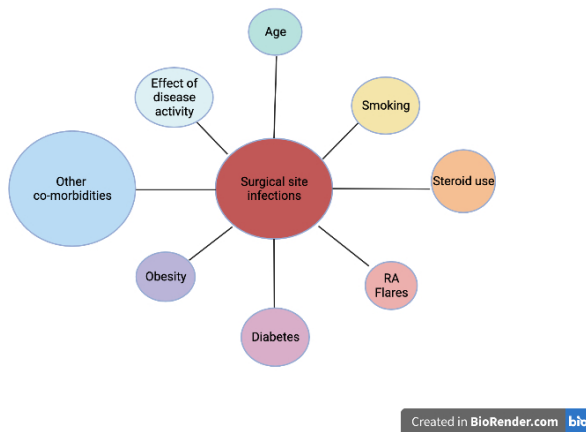


Fig. 4:

8.2. Interplay between TNF- α inhibitors and post-operative surgical site infections in RA

Before beginning treatment with anti-TNF- agents, doctors should try to get all patients immunised if at all possible. Live vaccines, such as influenza (nasal administration), oral polio, measles/mumps/rubella, yellow fever, and smallpox, should be administered cautiously. Immunization guidelines issued by the Centers for Disease Control and Prevention's advisory committee on immunisation practises generally advise against live attenuated vaccines in patients receiving immunosuppressive therapy until additional information is available. A newer, more conservative recommendation has recently been made regarding the zoster virus. For at least three months after stopping immunosuppressive therapy, live attenuated vaccines should not be given. Anti-TNF- therapy can be safely supplemented with inactivated vaccines.^{45,46}

9. Conclusions

In RA patients receiving anti-TNF- therapy, some studies have found an up to twofold increase in the risk of serious

infections; however, other studies have failed to find this link. In addition, even a twofold increase in infection risk is likely to be comparable to the glucocorticoid doses commonly used for RA patients. A reduction in glucocorticoid use may reduce the risk of infection associated with anti-TNF- therapy. Anti-TNF- therapy may be able to reduce the risk of infection by improving long-term inflammation control, but this has not yet been proven.

Discordant results between studies may be due to differences in patient populations, co-morbidities, DMARD use by patients who were not exposed to TNF- α antagonists, patterns of glucocorticoid use, and different analytical approaches. More transparency is needed in the assessment and reporting of adverse events, and standardising methodology may help harmonise the results of various investigations. In order to develop appropriate clinical practise guidelines and effectively communicate this information to patients, additional research is needed to assess relationships between infections and anti-TNF-therapy and newer biologics.

10. Conflicts of Interests

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