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Review Article

A systematic review on the impact of interventions on gene expression profiles of rheumatoid arthritis patients

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease with a poorly known aetiology. Although the primary characteristic of RA is inflammation, other biological systems are implicated in various phases of the disease. Interventions and their impact on gene expression in active RA patients is currently playing a significant role in the development of specific treat to target techniques. The present study aims to evaluate the effect of various reported interventions on gene expression in rheumatoid arthritis patients. Publicly available English databases, PubMed and Google Scholar, were queried from 2020 to 2023. We mined a total of 1970 research documents, of which 8 articles were selected based on the inclusion and exclusion criteria. The review analyzed therapeutics, including anti-TNF alpha-blockers, GM-CSF blockers, Chemokine receptor blockers and herbal Ginger in RA treatment and prediction of responders and non-responders based on gene expression analysis. However, due to the mixed-use of samples, experimental methodologies, analysis tools and genes studied in the studies, our comparison is inconclusive in determining effective therapy. The study highlights the necessity of harmonization in order for gene expression profiles to be effectively used as a clinical tool in RA patients' personalized medication.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition characterized by inflammation of the joints and, in rare cases, other body parts (eyes, lungs, heart, blood vessels and skin).[1] In RA, the immune system, which typically defends the body against infections, erroneously attacks the synovial membrane surrounding joints, thickening the synovium and destroying the joint's bone and cartilage. It usually affects the tiny joints in the feet and hands symmetrically, causing arthralgia, swelling, stiffness, and eventually joint degeneration and deformity if prolonged or untreated.[2,3] It predominately affects females aged 35 to 60 years compared to males in a ratio 4:1.[4] RA above 65 years is known as elderly onset rheumatoid arthritis (EORA). As age progresses, the ratio of females to males also decreases to 2:1.[5] The incidence and prevalence of RA vary based on geographical region, age and sex. The prevalence of RA was 208 cases per 100,000 people worldwide in 2020, accounting for 17.6 million cases.[6] In India, the prevalence rate ranged from 0.28 to 0.7%, accounting for 13 million cases.[7]

Rheumatoid arthritis has a complicated aetiology, with several environmental, immunological, genetic and other factors (age, sex) influencing disease progression

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and gene expression. Long before the onset of clinical symptoms, genetic (MHC shared epitope alleles) and environmental factors (smoking, high sodium intake) might interact to cause adaptive responses associated with autoimmunity and induce the production of peptidyl arginine deaminase (PAD).[8,9] PAD enzyme modifies proteins post-translationally by converting arginine to citrulline, thereby changing the structure and function of the modified protein. The antigen-presenting cells process these modified citrullinated proteins presenting as foreign antigens to T-cells, thereby stimulating antibody or autoantibody or anti-cyclic citrullinated peptide antibodies (ACPA) production.[10] Initially, immune cells are stimulated in the regions distant to synovial fluid and ACPA levels can be detected in the serum much before the onset of RA symptoms.[11,12] Over time, few individuals will ultimately develop immune-mediated inflammation primarily localized in the synovium. Within the synovial compartment, cytokines and chemokines (GM-CSF, IL-6, TNF) activate endothelial cells and attract immune cells, both innate (monocytes, mast and dendritic cells) as well as adaptative cells (Th-1, Th-17, B cells and plasma cells) into the compartment and activate fibroblast-like synovial cells (FLS). Proliferating in the synovium, cytokines are a major contributor to the severe inflammatory reaction that leads to cartilage loss and bone degradation. Progressive joint deterioration is caused by the migration of FLS from one joint to another.[13–15]

RA disease progression has been linked to its heterogeneity. Three types of synovial tissues-one with T cells, B cells, APC and MHC genes, second with stromal genes and third with mixed with both genes were observed.[16] Gene profiling studies showed clear distinctions in gene expression between early RA (<12 months) and late RA (>5 years) in synovial tissue, indicating the existence of various pathophysiological mechanisms throughout the disease course.[17,18] Using microchip analysis, distinct molecular markers and biological processes, including host defences, stress responses, T-cell-mediated immunity, MHC class II-mediated immunity, stress responses, host defences and tumour suppressors, and MHC class II-mediated immunity were observed at different stages of the disease.[19]

Despite documented RNA heterogeneity, the application of treat-to-target techniques in RA is poor, with most studies showing increased treatments in almost 50% of patients diagnosed with moderate or high RA.[20,21] To comprehend the effectiveness of treatment and the course of the disease, it is essential to look into how interventions affect the expression of certain genes in patients with rheumatoid arthritis (RA). These interventions frequently cover a wide range of treatments, from new biologics or developing targeted medicines to more conventional meds like disease-modifying ones. The present systematic review aims to evaluate the effect of interventions on gene expression in patients with rheumatoid arthritis.

2. Materials and Methods

2.1. Literature search

Using PRISMA- systematic review and meta-analysis guidelines, the present study search to evaluate the effectiveness of interventions on gene expression in rheumatoid arthritis patients was conducted.[22] The inclusion criteria for screening the research articles include randomized and observational studies to understand the association between interventions (medications) and gene expression in RA patients. The exclusive criteria include non-randomized studies, uncontrolled studies, laboratory studies and case reports. Literature searches are done only in English databases such as PubMed, Embase, and Google Scholar. Search was confined to a time period from 1995 to 2020. The main keywords for PubMed are rheumatoid arthritis, gene expression, gene profiling and interventions or therapeutic treatments. The pertinent medical subject headings (MeSH) used are (Arthritis, Rheumatoid"[Mesh] AND ("Gene Expression"[Mesh] OR "Gene Expression Profiling"[Mesh] AND "Interventions"[Mesh] OR "Medications"[Mesh] OR "Therapeutics"[Mesh]). To find other related studies, we thoroughly reviewed our options, selected the study with larger sample size or the most recent publication for our research samples, and then looked further into the publications' references to find comparable studies.

2.2. Selection and screening

The screening approach consists of research articles performed separately by two researchers. Research documents were screened in the first step based on the title and abstract. Based on the inclusion and exclusion criteria, the selected research documents were thoroughly reviewed and articles not meeting the inclusion criteria were excluded from the study. The research articles were excluded if the study was about rheumatoid arthritis gene profiling for diagnostics or rheumatoid arthritis therapeutics not targeted towards gene expression. Finally, the researcher independently retrieved pertinent data from the included studies using a pre-designed data-collecting form. Any differences in the data collected were sorted out through discussion. The primary contents of the data collection form include the title of the research article, author name, year of publication, study design, indication, inclusion and exclusion criteria of the selected article, sample size, study population, methodology, gene expression analysis methodology, expressions analyzed, targeted interventions, outcomes and conclusion of the study.

2.3. ROB analysis

For randomized studies, the ROB were assessed using JBI critical appraisal tools.[23] The subsequent queries were addressed to evaluate the bias.

1. Was proper randomization employed for allocating patients to therapeutic groups?
2. Were the treatment group blinded from allocation?
3. At the initial stages, were the treatment groups comparable?
4. Were participants concealed of their treatment regime?
5. Were physicians or nurses administering treatment blinded of the treatment assignment?
6. Did outcome assessors concealed from the treatment assignment?
7. Apart from the relevant intervention, were the treatment groups treated similarly?
8. Was follow-up done to the end, and if not, were the variations in follow-up between the groups sufficiently explained and examined?
9. Were the patients or participants assigned randomly to a group examined?
10. Were the treatment groups' outcomes evaluated identically?
11. Were results measured accurately?
12. Was relevant statistical analysis performed?
13. Did the study's conduct and analysis consider any modifications from the conventional RCT design, such as individual randomization and parallel groups, and was the trial design appropriate?

The overall rating for each question was rated as Yes (implies high quality), No (indicates quality or particular criteria not fulfilled) and Unclear (suggests particular criteria in the selected paper not accurate) (Table 1 Suppl).

3. Results

3.1. Literature search and study characteristics

A summary of the systemic review search strategy with inclusion and exclusion articles was presented in a flowchart (Figure 1). From English databases, 1970 studies were retrieved, 40 duplicates were discarded. After the initial article title and abstract screening, 1890 were excluded. Further, in the full-text analysis, 32 non-relevant articles were excluded, and 8 research articles were selected for the final study. All the selected studies were randomized controlled studies.[24–31] Among these, one of the study was a randomized controlled non-placebo study,[25] 4 were randomized double-blinded placebo-controlled trials,[26,29–31] 1 study was stratified randomized[27] and 1 was randomized open-label study.[28] The cumulative sample size of the present study was 557. Table 2 shows the study characteristics of the selected studies.

3.2. Gene expression analysis analytical techniques

Molecular techniques commonly used in the selected studies were quantitative reverse transcriptase PCR (qRT-PCR) and microarray techniques.[25–29,31] Immunohistochemical analysis was conducted by.[26,30] Quantitative cytokine analysis was performed using integrated optical density.[30] Anti-TNF blockage was quantitively analyzed using dynamic contrast MRI.[29] Whole blood or peripheral blood mononuclear cells were commonly used to analysize the gene expression[25–31] whereas 2 studies used synovial tissue for their studies.[24–26]

3.3. Interventions and their outcomes

Traditional herbs like Ginger (1500 mg/daily) were supplemented to active RA patients to study immunity factors and intermediate gene expression. After 12 weeks of intervention, an increase in transcription factor (FoxP3; GATA3) and antiinflammatory factors PPAR-γ whereas a decrease in inflammatory factors such as T-bet, RORγt and NFκB was observed.[31] Methotrexate was able to decrease the expression of pro-inflammatory cytokines (IL-12A; IL-6)[27] and in combination with prednisone was significantly able to reduce serum TNF-α levels in active RA patients.[25] Similarly, infliximab therapy showed respondents had high Ktrans and low B-cell expression compared to non-respondents. However, a study showed that only anti-TNFα therapies like infliximab and MTX were insufficient in rheumatoid arthritis treatment.[29] Also, only anti-CCR2 antibodies targeting chemokine CCR2 receptor present on monocytes and T-subset cells were found not to decrease synovial inflammation in active RA[26] whereas rituximab (RTX), a chimeric monoclonal anti-CD20 antibody targeting CD-20 found the B-cell surface was found to downregulate B-cell gene expression. RTX can also used in diagnostic differentiation between responders and non-responders based on the signature of upregulation of NF-kB genes and downregulation of interferon genes.[28] Mavrilimum, a human monoclonal antibody targeting the α-subunit of GM-CSF receptor, was reported to decrease the T-cell and myeloid gene expression and indirectly suppress IL-2 α receptor and IL-17/IL-22mRNA expression.[30] Lastly, gold therapy singly or combined with methylprednisolone acetate decreased endothelial leukocyte adhesion molecule 1 expression levels and synovial blood vessels (Table 3).[24]

Table 1: Suplementary ROB analysis of the included studies

1.	**Was proper randomization employed for allocating patients to therapeutic groups?**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
2.	**Were treatment group blinded from allocation?**	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
3.	**Were treatment group blinded from allocation?**	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
4.	**Were participants concealed of their treatment regime?**	Unclear	Yes	Yes	Yes	No	Unclear	Yes	No
5.	**Were physicians or nurses administering treatment blinded of the treatment assignment?**	Yes	Yes	Yes	Yes	No	Unclear	Yes	No
6.	**Were physicians or nurses administering treatment blinded of the treatment assignment?**	Yes	Yes	Yes	Yes	No	Unclear	Yes	No
7.	**Apart from the relevant intervention, were the treatment groups treated similarly?**	Yes	Yes	Yes	NO	Yes	Yes	No	Yes
8.	**Was follow-up done to the end, and if not, were the variations in follow-up between the groups sufficiently explained and examined?**	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9.	**Were the patients or participants assigned randomly to a group examined?**	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
10.	**Were the treatment groups' outcomes evaluated in an identical manner?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
11.	**Were the treatment groups' outcomes evaluated in an identical manner?**	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
12.	**Was relevant statistical analysis performed?**	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13.	**Did the study's conduct and analysis take into consideration any modifications from the conventional RCT design, such as individual randomization and parallel groups, and was the trial design appropriate?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	References	31	27	29	26	28	24	25	30

Table 2: Study characteristics of the present study

Title	Sample size (n)	Study design	Inclusion criteria	Exclusion criteria	Reference
The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis	70	Randomized double blinded placebo controlled trial 1. Ginger (n=35) 2. Placebo (n=35)	1. Active RA patients (19 to 69 years) 2. 2 years of disease duration, 3. Treatment with < 10 mg/day of hydroxychloroquine, methotrexate and prednisolone 4. Not treated with antiinflammatory drugs	1. Patients with history of myocardial infarction, hyperlipidemia, abnormal renal or hepatic function and hyperlipidemia 2. Patients on mineral and vitamins supplements 3. Patients on medications such as anti-hypertensive drugs, thyroid hormones, contraceptives, and β-blockers 4. Patients with history of smoking and alcohol use 5. Pregnant and lactating women	[31]
The influence of methotrexate on the gene expression of the pro-inflammatory cytokine IL-12A in the therapy of rheumatoid arthritis	17	Stratified randomized 1. Methotrexate 15 mg (n=9) 2. Methotrexate 25 mg (n=8)	1. MTX-naïve patients 2. Newly diagnosed RA patients	1. Patients with a former MTX use 2. Pulmonary, HIV, hepatitis B and C) diseases 3. Low disease activity (≤3.2) 4. Contraindications for MTX	[27]

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Table 2 continued

Pre-treatment whole blood gene expression is associated with 14-week response assessed by dynamic contrast enhanced magnetic resonance imaging in infliximab-treated rheumatoid arthritis patients	61	Randomized double blinded placebo controlled trial 1. Infliximab 3 mg/kg in 0.9% NaCl (n=30) 2. Placebo- 0.9% NaCl alone (n=31).	1. Patients with 6 months of RA diagnosis 2. Has at least 6 swollen and tender joints 3. Has CRP ≥ 10 mg/L, ESR ≥ 28 mm/hr 4. MRI evidence of synovitis 5. Received methotrexate therapy for ≥ 3 months 6. A stable combinational dose disease modifying anti-rheumatic drug (DMARD) with methotreate in combination with methotrexate must be on a stable dose	1. Pregnant and lactating patients 2. Patients with inflammatory arthritis 3. Patients with history of hypertension, heart problems, renal, hepatic, neurological and other organ related diseases or problems 4. History of tumor or carcinoma 5. Bacterial and viral infections 6. Hypersensitive to immunoglobulins or infliximab or rituximab	[29]
Modulation of CCR2 in Rheumatoid Arthritis	32	Randomized double blinded placebo controlled trial 1. Anti-CCR2 antibody 0.5 mg/kg (n=7) 2. Anti-CCR2 antibody 1.5 mg/kg (n=7) 3. Anti-CCR2 antibody 4 mg/kg (n=9) 4. Placebo (n=9)	1. Patients ≥ 18 years 2. Patients with 6 months of RA diagnosis 3. Has at least 4 swollen and tender joints 4. 1 actively inflamed knee or ankle joint, or wrist 5. Has CRP 15 mg/L, ESR ≥ 28 mm/hr 6. Received combination therapy with methotrexate for 4 months before screening	1. Patients using DMARDs, prednisone, leflunomide, infliximab, adalimumab, etanercept continuously 2. Physically incapable patients 3. Any other medical conditions 4. Other major inflammatory disease	[26]

Continued on next page

Table 2 continued

Use of whole-blood transcriptomic profiling to highlight several pathophysiologic pathways associated with response to rituximab in patients with rheumatoid arthritis: data from a randomized, controlled, open-label trial	68	Randomized open label	1. Patients >18 years 2. RA for ≥6 months 3. Has at least 6 swollen and tender joints 4. Has CRP ≥ 10 mg/L, ESR ≥ 28 mm/hr 5. Treatment with methotrexate for ≥3 months, stable dosage for ≥1 month	1. Prior therapy with MabThera 2. Combinational therapy with anti TNF-α therapy 3. Prior biological or cell-depleting therapies	[28]
Gold treatment of rheumatoid arthritis decreases synovial expression of the endothelial leukocyte adhesion receptor ELAM-1	-	Randomized trial	-	-	[28]
Combination therapy with cyclosporine and methotrexate in patients with early rheumatoid arthritis soon inhibits TNFalpha production without decreasing TNFalpha mRNA levels. An in vivo and in vitro study	24	Randomized controlled non-placebo study 1. Prednisone + methotrexate 2. (n=12) cyclosporine (n=12)	1. Patients who met the revised American Rheumatism Association guidelines 2. Had RA < 2 ye a rs; and 3. No prior DMARD therapy	1. Patients with prior history of hypertension, hepatic or renal abnormalities, platelet count 2. Having combinational therapy with experimental drugs	[25]
Blockade of GM-CSF pathway induced sustained suppression of myeloid and T cell activities in rheumatoid arthritis	305	Randomized double blinded placebo controlled trial	1. Patients >18 years 2. RA for ≥6 months 3. Has at least 4 swollen and tender joints 4. Has CRP ≥ 10 mg/L, ESR ≥ 28 mm/hr 5. Treatment with methotrexate (7.5 to 25mgg week), stable dosage for ≥1 month	1. Patients with prior treatment with biological DMARDs, steroids, alkylating drugs, combinational therapy (DMARDs + methotrexate) 2. Patients with cuncontrolled respiratory disease, infections and untreated latent tuberculosis	[30,32]

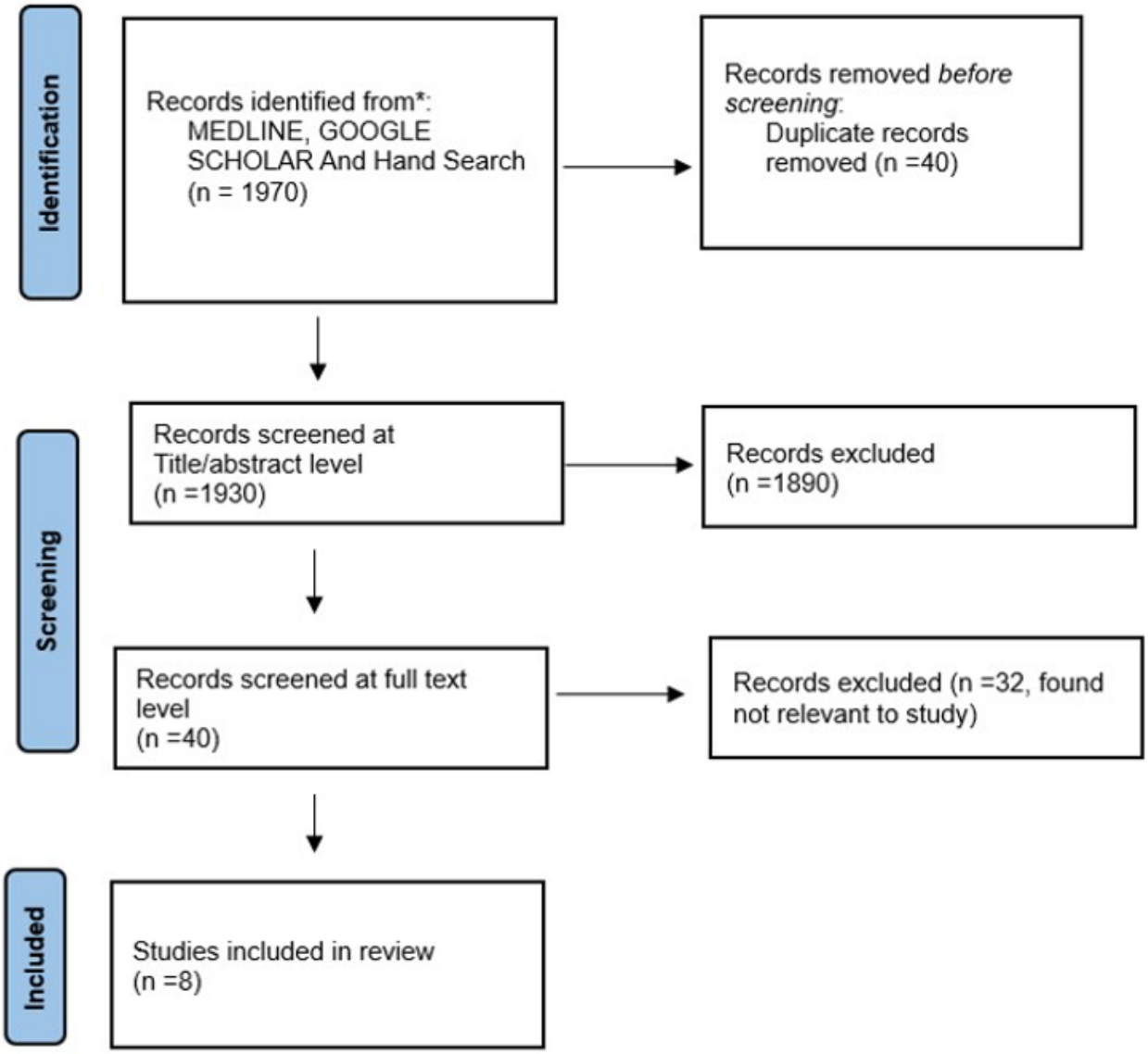

Figure 1: PRISMA flow diagram for the systematic review which included searches of databases

Table 3: Interventions and outcomes of the included 8 studies

Intervention	Sample	Analytical technique	Gene expression or biomarkers analyzed	Results	Conclusion	Reference
Ginger supplementation	Peripheral blood mononuclear cells	qRT-PCR	f NF-κB, PPAR-γ, FoxP3, T-bet, GATA-3, and RORγt	1. ↑ FoxP3 and PPAR-γ genes expression in ginger group 2. ↓T-bet and RORγt genes expressio 3. After intervention, the reduction in disease activity reduction score ($p< 0.5$) was statistically significant between placebo and ginger group	Traditional medicine ginger can treat RA by specially decreasing T-bet and RORγt and increasing FoxP3 gene expression	[31]
Methotrexate (MTX)	Peripheral blood mononuclear cells	RT-PCR	IL-6 and IL-12A	1. MTX reduced of IL-6 and IL-12A expression 2. Combination therapy (MTX + corticosteroids) reduced IL-18 3. Correlation of 2566 gene scores with improved Ktrans score in infliximab treated patients whereas decrease Ktrans score in placebo patients. 4. B-cell gene expression low in patients responded to the treatment whereas high in non-responded patients 5. B-cell gene expression in respondents was consistent with monocytes and neutrophil mobiliztion	The study showed MTX decreased IL-12 gene expression thereby further reducing neutrophils and lymphocytes production.	[27]

Continued on next page

Table 3 continued

Infliximab	Whole blood	RNA extraction, RT-PCR, Microarray analysis	256 genes	1. Correlation of 2566 gene scores with improved Ktrans score in infliximab treated patients whereas decrease Ktrans score in placebo patients. 2. B-cell gene expression low in patients responded to the treatment whereas high in non-responded patients 3. B-cell gene expression in respondents was consistent with monocytes and neutrophil mobiliztion	These findings lend credence to the theory that anti-TNF α non-responders have RA pathology and molecular level gene expression compared to respondents of anti-TNF α therapy.	[29]
Anti-CCR2 antibody	Synovial tissue	Immunohistochemical analysis, Staining using immunoperoxidase, quantitative computer-assisted image analysis. cytokine expression estimated using the integrated optical density	1. Fibroblast-like synoviocytes (CD55) 2. T cells (CD3, CD4, and CD8) 3. Macrophages (CD68, CD163) 4. B cells (CD22), cytokines-TNF, interleukin -(IL-1, IL-6) 5. Free CCR2	1. Anti-CCR2 therapy reduced free CCR2 from 57 to 94%. 2. No reduction observed in all other synovial biomarkers. 3. No improvement was observed clinically.	Anti-CCR2 blocking antibody treatment did not reduce synovial inflammation in active RA patients. The findings refute the theory that CCR2 blockage alone could be enough to improve RA patients' clinical conditions.	[26]

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Table 3 continued

Rituximab (RTX)	Peripheral blood mononuclear cells	qRT-PCR, microarray assay	198 genes	1. 198 genes with substanitial baseline differenetial gene expression identified. 2. Of these 143 genes on 24 week, categorized patients as responders and non-responders based on their EULAR response data. 3. Post 24 week RTX treatment interferone pathway and B cell gene expression downregulated.	The study based on gene expression analysis could insight into identification of RTX non-respondents in active RA.	[28]
Gold and methylprednisolone acetate	Synovial tissue			1. After 2 and 12 weeks of treatment, there was a decrease in the expression of endothelial leukocyte adhesion molecule 1 (ELAM-1) on synovial blood vessels 2. The amount of neutrophils in the synovial membrane also decreased 3. Conversely, there was no discernible shift in the quantity or distribution of T cells within subsets, or in the expression of Class II MHC by endothelial, mononuclear, or synovial lining cells.	The findings conclude that one of the initial consequences of intramuscular gold and glucocorticoid therapy might be a reduction in the acute inflammatory response linked to the transcription of a neutrophil adhesion receptor on endothelium and the subsequent influx of neutrophils into the joint.	[24]

Continued on next page

Table 3 continued

Combination therapies-methotrexate (MTX), prednisone (PDN) and cyclosporine (CSA)	Peripheral blood mononuclear cells	RT-PCR	TNF mRNA	1. Post one month with MTX decreased TNF-alpha levels in group A (MTX25 mg/week) and group B (CSA 3.5mg/week. 2. Post 30 days on PHA stimulation group B had much lower TNF-alpha levels compared to group A.	Invitro, When CSA is added to a PDN + MTX therapeutic regimen, TNFalpha production is reduced without changing its mRNA expression. This impact may contribute to the initiation of early immunosuppressive and therapeutic outcomes in RA.	[25]
Mavrilimumab	Whole blood	Protein immunoassay and whole genome microarray	IL-22/IL-17 signalling pathways after GM-CSF	1. Treatment with Mavrilim resulted in ↓P4NP 7S, CCL22, IL-2 receptor α and IL-6 2. GM-CSF blockage resulted in reduced IL-22/IL-17 signalling pathways 3. Reduced myeloid and T cell-mRNA expression 4. The downregulation of genes linked to IL-17/IL-22 and the IL-2 receptor α indicates that mavrilimumab can indirectly T cell activation.	Our findings showed a correlation between alterations in peripheral biomarkers and RA patients' therapeutic response to mavrilimumab. Mavrilimumab's long-term effectiveness in RA may be due to its direct effects on myeloid cells as well as its indirect effects on T cell activation following GM-CSFR inhibition.	[2]

3.4. ROB analysis

Randomized studies RoB analyses showed that the included research publications had sufficient qualitative standards. Nevertheless, two studies' participants or physicians or outcome analyzers were not blinded to the treatment[28,30] and two studies were unclear in the blinding strategy applied.[24,31]

4. Discussion

The molecular fingerprints underpinning human disease are represented by gene expression profiles, which can predict an outcome with the highest likelihood of success. Due to the heterogeneous nature of rheumatoid arthritis, research into putative RA biomarker genes may lead to the discovery of new therapeutic targets for rheumatoid arthritis susceptibility.[33] The present study has revealed that a range of therapy modalities, such as biological and targeted therapies and disease-modifying anti-rheumatic medications (DMARDs), might affect the expression of specific genes in patients with active RA and also help in the differentiation of respondents and non-respondents to the specific therapy**.**

4.1. DMARDs agreement and disagreement with other studies

Cost-effective DMARDs such as methotrexate singly or in combination with prednisone were able to decrease serum TNF alpha levels as well as decrease the IL6 and IL-12A mRNA expression without any use of corticosteroids.[25,27] Although MTX is still used as the first line of therapy for RA treatment, MTX therapy alone is not sufficient to treat active RA. Studies showed in due course, the MTX therapy was discontinued due to secondary infections, gastrointestinal toxicity and hepatotoxicity as it also suppresses immunoglobulin production.[34] Also, studies could not identify any biomarkers or prediction models that could have predicted the response of MTX based just on baseline measures.[35]

4.2. Biological and targeted therapy agreement and disagreement with other studies

Biological therapy-anti CCR2 antibodies are insufficient for the active RA treatment due to low expression and redundancy of the CCR2 chemokine receptor. In addition to CCR2, monocytes synthesize other CCR chemokine receptors (CCR1, CCR5); thus, CCR2 blockage can be bypassed by the activity of other receptors. Combinational antibody therapy for all chemokine receptors must be developed for effective treatment.[26,36] Previous studies on anti-TNF α using infliximab were not consistent as each reported a different set of gene expressions either due to differences in techniques used like microarray, q-RT PCR or sample selected, thus making it difficult to distinguish between responders and non-responders.[37] A study conducted by MacIsaac et al., 2014 employed dynamic contrast enhance MRI to obtained a pre-treatment whole blood gene expression signature, which was correlated with a shift in the imaging biomarker Ktrans. The signature was linked to improved Ktrans in patients receiving infliximab but a decline in Ktrans in the placebo group.[29] However, further studies are required using Ktrans as an end biomarker in identifying respondents and non-respondents to anti-TNF alpha therapy. GM-CSF blockage therapy using the monoclonal antibody mavrilimumab was effective in RA treatment by suppressing the chemokine and interleukin genes involved in inflammation.[30] No adverse effect was detected, and clinical studies are going on in the commercialization of mavrilimumab treatment.[38]

4.3. Herbal therapy

Ginger was found to decrease the expression of inflammatory genes (T-bet and RORγt genes) and upregulation of antiinflammatory genes (FoxP3, PPAR-γ). Also, the DAS-28 score decreased significantly on 12 weeks of therapy.[31] Herbal medicines can serve as a substitute for allopathic pharmaceuticals in the treatment of RA patients, providing an alternate means of addressing the limitations of current therapeutic approaches. However, Ginger should be used cautiously by those on anticoagulants. There were currently no suggested safe and efficient dosages available.

5. Conclusion

Targeted interventions can significantly impact gene expression in active RA patients and help in early diagnosis and prognosis of RA disease. The present study makes it rather evident that gene expression profiling has a lot of promise for comprehending the biology of RA. Nevertheless, individual variation in treatment responses and gene expression profiles highlights the complexity of RA, prompting continuing study to elucidate the precise effects of interventions on gene expression and generate more personalized and successful therapeutic options.

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