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Tocilizumab Reduces Depression Risk in Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis

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Abstract: Depression is a possible cause of the increased mental health risks associated with rheumatoid arthritis (RA), including depression-related complications. Biological disease-modifying antirheumatic drug (bDMARDs) therapies have emerged as innovative anti-inflammatory drugs with positive effects on mental well-being. Tocilizumab is a bDMARDs commonly used to treat RA and its influence on depression needs to be studied. It targets interleukin-6 (IL-6) receptors, reducing inflammation, which may also alleviate depressive symptoms due to the role of inflammation in the pathophysiology of depression. Thus, its influence on depression needs to be studied. To assess the strength of the association between exposure to tocilizumab and the rate of development of depression in patients with RA and to evaluate tocilizumab as an exposure and depression as an outcome in these patients, a search was conducted in the MEDLINE, PreMEDLINE, Cochrane, and Scopus databases from January 1980 to April 2024. Inclusion criteria were studies that diagnosed RA according to the latest American College of Rheumatology/European League Against Rheumatism guidelines or a rheumatologist and provided information on tocilizumab exposure and diagnosed depression as an outcome. The present meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. These studies were assessed for eligibility by the author and an independent assessor. To summarize the findings, the meta-analysis combined the relative risk estimates from each study with raw data counts. Twelve studies in the meta-analysis fulfilled the inclusion criteria. Tocilizumab monotherapy exhibited a promising beneficial effect on the risk of depression, indicated by the decreased risk in RA patients (Relative risk 0.68, 95% CI 0.20, 2.31). Patients with RA on tocilizumab treatment had a lower risk of developing depression compared to those unexposed to tocilizumab treatment. Therefore, future longitudinal studies are needed to confirm the beneficial effect of tocilizumab on depression in the RA population.

Keywords: rheumatoid, Actemra, depression, traditional DMARDs, biologic DMARDs

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease estimated to affect 1% of the global adult population.[1] Erosive-destructive RA is characterized by progressive erosion and destruction of joint structures, leading to irreversible joint damage, deformity, functional impairment and disability. Along with physical challenges, many patients with RA experience mental health issues, including depression.[2] The prevalence of anxiety and depressive disorders among patients with RA was 25.1% and 17%, respectively.[2,3] The prevalence of depression in the general population is 5%[2] The incidence rate ratio (IRR) for major depressive disorders significantly increased in patients with incident RA compared to the general population (IRR 1.46, 95% confidence interval [CI] 1.35, 1.58).[4] Uncontrolled depression in patients with RA was associated with several deleterious complications, including an increased risk of disability, reduced physical function and quality of life, and an increased mortality rate.[5]

New evidence suggests a common inflammatory pathway between RA and depression. Inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), may be elevated in patients with depressive disorders.[6]

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Treatments for RA that target TNF inhibitors (TNFi) may improve the mental health outcomes of patients with depression who have chronic physical illnesses[7] and high levels of inflammation.[8]

Over the past 25 years, RA management has evolved and is characterized by earlier diagnosis, and earlier, more aggressive treatment. The framework of the "treat-to-target" method emphasizes that the ultimate goal is to reach remission and that medication should be changed until the target is achieved.[9] The typical medical course of action in the early stages of treatment involves administration of traditional synthetic disease-modifying antirheumatic drugs (tDMARDs), predominantly methotrexate (MTX). Targeted biologic DMARDs (bDMARDs), which are more expensive, were previously reserved for patients who did not respond sufficiently to at least two tDMARDs. However, the latest guidelines recommend that adults with active RA should be managed with the intention of achieving remission or minimizing disease activity; if remission is not possible, using the treat-to-target method. This may require the use of multiple tDMARDs and bDMARDs in sequence, each with its own mode of action.[10] Over the past few decades, a large number of novel bDMARDs have been developed,[11] which block different cytokines and immunological messengers. They influence disease behavior and may affect a patient's psychological condition, although evidence to support this finding is in the early stages.

The use of bDMARDs has not been associated with an elevated risk of demyelinating disorders or neurolupus; rather, it may confer therapeutic advantages in coexisting conditions.[12] Abatacept and rituximab are potential treatments for refractory chronic inflammatory demyelinating polyneuropathy,[13] with encouraging outcomes seen in multiple sclerosis trials.[14] While one case report suggested a link between tocilizumab (TCZ) and new-onset multiple sclerosis in a patient with RA, symptoms improved upon discontinuation of the drug;[15] another case report demonstrated the safety of TCZ in a patient with RA and inactive multiple sclerosis.[16] Emerging evidence suggests that TCZ may be effective in treating neuromyelitis optica.[17] New bDMARDs may decrease symptoms of depression in patients with RA, despite conflicting data on the effect of tDMARDs on psychiatric illnesses.[18] A comparison of the prevalence of depression and anxiety in patients with RA taking various DMARDs, showed that treatment with bDMARDs, such as TNF antagonists, resulted in more patients with higher depression scores than those treated with tDMARDs (MTX and hydroxychloroquine).[18]

Emerging evidence shows patients on TCZ may have decreased depression symptoms. TCZ is a bDMARDs that targets the IL-6 receptor and is recognized as an effective treatment for alleviating RA symptoms.[19] Some randomized control trials have shown that TCZ improves mental health in patients with RA, as measured by a Beck Depression Inventory-II (BDI-II) questionnaire for RA scores when compared to saline and adalimumab (TNF-blocker drug).[20,21] However, there is no conclusive evidence regarding the effects of bDMARDs (specifically TCZ) on depression among patients with RA, and most studies assessed the prevalence of depression among the RA population.

Therefore, this study aims to systematically review and analyze available evidence about the effect of TCZ on improving depression outcomes in patients with RA. The primary objective is to investigate the effect of TCZ monotherapy exposure on reducing the risk of depression in RA. The secondary objective is to examine the additional benefits of TCZ combination therapy (combination with MTX) compared with TCZ monotherapy, in reducing the risk of depression in the RA population and to investigate the potential implications of factors that affect depression outcomes, such as patient demographics, and RA severity and duration.

Materials and Methods

The present systematic review and meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.

Search Methodology

A literature search was conducted for articles on the relationship between TCZ and depression among patients with RA on the PreMEDLINE, MEDLINE, Scopus, and Cochrane databases, from January 1980 until April 2024. The PreMEDLINE and MEDLINE databases were searched using PubMed. Articles were identified using controlled vocabulary terms, Medical Subject Headings (MeSH terms) as well as keywords (S1 Appendix). The citation lists of relevant articles were hand searched to look for additional papers.

Study Selection and Patient Outcomes

The exposure of interest was TCZ (®ACTEMRA) monotherapy for at least 4 weeks. The comparison group was patients with RA not taking TCZ (either TCZ naive or taking other tDMARDs or bDMARDs) and patients with RA using TCZ in combination with MTX were included for additional analysis to compare the additional effects of these combinations with TCZ monotherapy on the development of depression.

The primary outcome was the rate of depression defined by the presence or absence of depression diagnosed by a physician's clinical diagnosis using a standardized depression scoring scale. Per patient data was calculated as the number of patients with RA who had depression out of the total group studied over the follow-up period.

Following good practice for systematic reviews and meta-analyses, the search, selection, and extraction steps were conducted in blinded pairs, the author and an independent assessor (an assistant professor and senior researcher at King Saud University) independently evaluated the articles for eligibility, study selection, and quality assessment.

The inclusion criteria for studies in this meta-analysis were diagnosis of RA in adult patients (≥18 years) according to current American College of Rheumatology (ACR)/European league against rheumatism (EULAR) guidelines or by a rheumatologist, documented TCZ exposure, assessment of the outcome of interest (depression) based on a physician's clinical diagnosis using a standardized depression scoring scale, and reported raw count data. Exclusion criteria were unfulfilled inclusion criteria, no available information about the patients' TCZ exposure, no available information about the patients' outcome (depression), and unavailable required raw count data.

Data Extraction

Data from each study was summarized in terms of study design, country where study was conducted, participants' characteristics, the assessed TCZ exposure (details of non-TCZ DMARDs), assessed outcome, and study quality score (Qi).

Quality Scores of Included Studies

The studies included in this meta-analysis use a range of methodological approaches and various study designs. Therefore, it was crucial to consider the quality of the combined research. The studies included for this meta-analysis were critically evaluated using a validated and replicable checklist (S2 Appendix). This instrument was practical and efficient for separating high-accuracy and low-bias studies from those of lower quality[22–25] and enabled the calculation of a quality index (Qi) for each study. Using 14 questions to assess the internal validity, external validity, and statistical analysis of the research, this checklist assesses the quality of each study (S2 Appendix).[24] To calculate the Qi number, each item on the checklist was assigned a point value. Question 9 in the checklist was tailored to accommodate the requirements of this study and assessed the prognostic factors. This question was tailored to balance the factors influencing depression results across exposure groups. These prognostic factors include age, sex, socioeconomic status, access to healthcare/health insurance, physical inactivity, duration of RA, and use of medications such as folic acid and corticosteroids. A score of 1 was given, if the study balanced ≥5 of these prognostic indicators across comparative groups. The study received a score of 0.5, if it reported 3–4 of these prognostic indicators, 0.5 if it weighed just one or two of these prognostic factors and a score of 0, if there was no proof that any of these prognostic variables were reported. Each study was critically reviewed and points awarded for each correct answer. The total points were added up to determine the Qi score. A Qi score of ≥10 was considered to be a good quality study, while a Qi score of ≤9 was considered to be a poor quality study.

Statistical Analysis

The association between exposure to TCZ and development of depression was assessed by conducting meta-analyses using MetaXL software version 5.3 (EpiGear International, Brisbane, Queensland, Australia). Meta-analyses were obtained using a quality effects model (QE), and comparisons were made using a random effects model (RE). The QE model has an advantage over the RE model because it accounts for the study-level risk of bias and adjusts for the quality of included studies.[26]

Raw counts for exposed and unexposed groups as well as event and non-event RA groups were used to determine effect sizes and confidence interval (CI) for the depression outcomes. An event was defined as an occurrence of incidental or prevalent depression. As the outcome of interest is binary (with depression or without depression), relative risk (RR) was used to measure the association between the exposure to TCZ monotherapy and the development of depression in the RA population. RR was calculated separately to examine the additional benefits of TCZ combination therapy (combination with MTX) compared with TCZ monotherapy in reducing the risk of depression in the RA population. While an RR value of 1 indicates equivalence, an RR value <1 indicates a reduced risk of developing depression in patients with RA exposed to TCZ compared to patients with RA not taking TCZ.

The Q-statistic and its variations have poor statistical strength when used to test for heterogeneity. Therefore, when combining the findings of various studies, another strategy must be added to the statistical methods. This additional strategy involves checking for heterogeneity while remaining alert, using common sense, and employing previous biological knowledge.[27] If the value of tau-squared was <0 and/or the Q-statistic was significant ($p < 0.1$), it was predicted that statistical heterogeneity existed between the research groups.

Statistical heterogeneity was evaluated using the I2 statistic. This test measures the proportion of the overall variance among the included studies that was caused by heterogeneity rather than chance; if the value of I2 is 50% or higher, a significant degree of heterogeneity is observed.[28] When heterogeneity was documented, potential influential factors were assessed, including the length of follow-up, age, methods of TCZ assessment, methods of depression assessment, use of antirheumatic medications, number of recruited patients with RA, and the percentage of included males compared to females. The effect of TCZ monotherapy exposure on the development of depression among patients with RA was further analyzed by subgroup analysis. The probable modifying effects of the various characteristics of patients with RA included in the research were investigated. Factors considered include age, RA duration, follow-up period, depression diagnosis, duration of TCZ monotherapy exposure, RA disease activity assessed by the Disease Activity Score 28 (DAS-28) or Clinical Disease Activity Index (CDAI), use vs no use of corticosteroids, and publication year and country. Subgroups were identified based on the mean age of patients with RA (≤55 years or >55 years), mean RA duration (≤7 years or >7 years), follow-up time (≤1 year or >1 year), study design (prospective cohort or non-cohort), depression diagnosis (by standardized depression score, history or self-report), onset of diagnosing depression (pre-existing or newly diagnosed depression), duration of exposure to TCZ monotherapy (≤1 year or >1 year), RA disease activity measurement by DAS28 or CDAI (measured or not measured), level of RA severity (moderate or high RA severity), use vs no use of corticosteroids, publication year (before/during 2020 or after 2020), and country of publication (North America [USA], Middle East, and Europe). To evaluate potential publication bias, a funnel plot was created by plotting the effect measure against its standard error's inverse, and an Egger's test of intercept was used.[29] Asymmetry in the plot and $p < 0.05$ indicated statistically significant publication bias.

Results

Search and Screening

A comprehensive search of the PreMEDLINE, MEDLINE, Scopus, and Cochrane databases yielded 1,668 studies, and two additional published studies were discovered through meticulous hand searching. After elimination of duplicates (280 studies), there remained 1,390 studies published between January 1980 and April 2024. Upon examining the abstracts of these publications, 1,204 were discarded as they failed to meet the inclusion criteria, leaving 186 studies for consideration (Figure 1). These 186 articles were thoroughly evaluated and assessed for their eligibility and 174 studies were excluded due to insufficient information. Of these, 168 articles lacked details on TCZ exposure and other non-TCZ DMARDs, three articles contained no information on depression, and three articles had no data on RA.

Therefore, 12 studies that met the inclusion criteria were incorporated in qualitative and quantitative analyses.[21,31–41] Of these, four studies evaluated depression in the RA population and reported the effect of TCZ combination with MTX vs TCZ monotherapy in reducing the risk of depression in the RA population.[31–33,38]

Most included studies assessed depression as one of the main outcomes (n=7) except for a few studies that considered depression as a TCZ adverse effect on mental health in RA (n =5).[21,31–33,38] We conducted a thorough examination of these studies to acquire useful data about TCZ exposure and its effects on depression in patients with RA. We rigorously

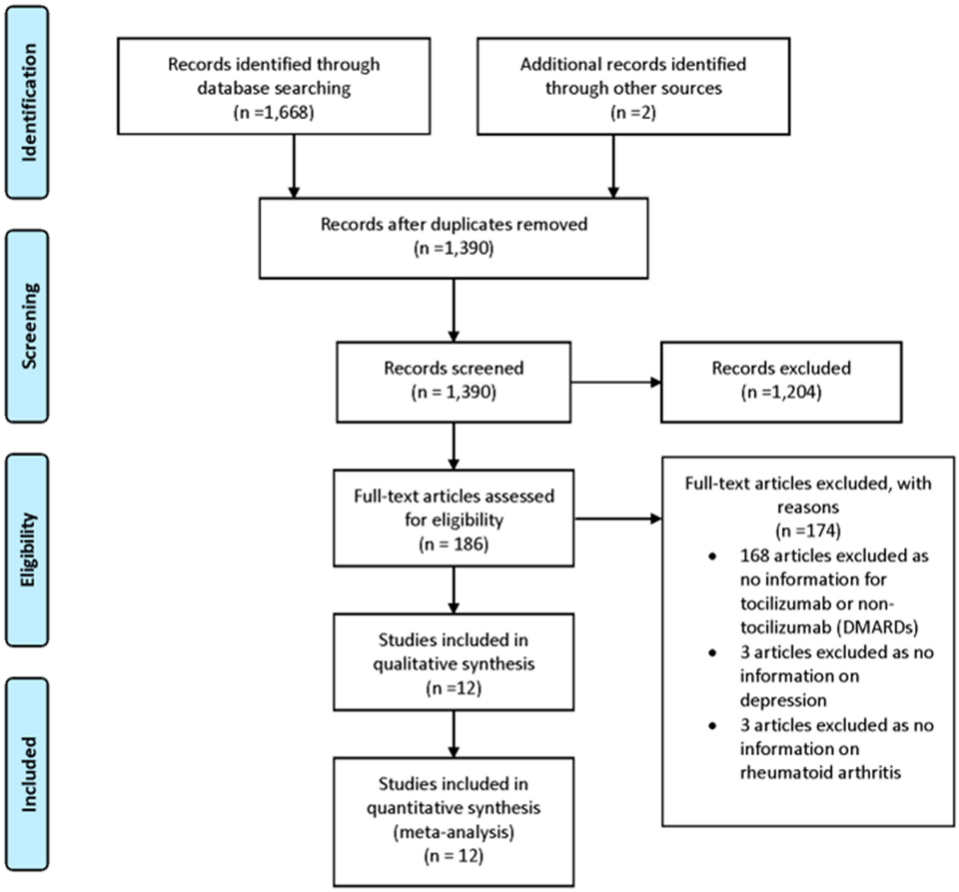

Figure 1 Prisma flow diagram. *From*: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6 (7): e1000097.[30]

evaluated the 12 studies and obtained raw data for patients with RA exposed and unexposed to TCZ, along with event and non-event groups. They provided data on 4,404 patients with RA exposed to TCZ monotherapy and 4,777 patients with RA not exposed to TCZ.

Characteristics of Studies and Subjects

The details of the 12 eligible studies incorporated into this systematic review and meta-analysis are in Table 1. These studies display substantial variation in terms of research design, methodological rigor, patient age, illness duration, application of antirheumatic medications, and determination of TCZ exposure and depression outcomes. Among the included articles, three studies had a cross-sectional design,[34,35,40] five were prospective cohort studies,[21,36,37,39,41] and four were randomized controlled trials.[31–33,38] The publications' country of origin varied among the studies analyzed. Four studies focused on patients with RA in North America, specifically in the USA,[31,33,37,41] three studies were conducted in the Middle East, including Saudi Arabia[34,35] and Israel.[21] One study was conducted in Asia (within Taiwan),[40] and two studies were from Europe (Germany and UK).[36,39] There were two multicenter studies and recruited patients with RA from 14[38] and 18[32] countries, respectively.

The quality of the studies varied significantly, with Qi scores ranging from 9[21,36,40] to 14.[31] The average age of patients with RA varied from 51 years[33] to 62 years.[40] Patients included in this systematic review had established RA and the RA duration ranged between 3.1 years (0.6–9.4 years)[33] and 12.6 ± 9.7 years.[39] Although early RA (mean RA duration <1 year) was examined in one of the studies,[31] data were obtained during the follow-up period (2 years), which indicated that patients had established RA. Most of the studies measured RA activity by DAS28 or CDAI except three studies did not considered the RA activity,[34,35,41] with a mean score indicating moderate to high RA activity based on the 2019 update of the ACR recommendations.[42] Although each research article documented the exposure to TCZ and the subsequent development of

Table 1 Studies Included in the Quantitative Meta-Analysis (n = 12)

Reference	N	Study Design	Country	Participants	TCZ monotherapy exposure assessed	Non-TCZ DMARDs and corticosteroids assessed	Depression Outcome	Qi score out of 14
(Ng et al, 2020)[40]	Total RA patients 625 (females 489, males 136)	Cross-sectional	Taiwan	RA diagnosed according to ACR/EULAR criteria; mean age: 62.1± 13.5 years; RA duration: majority >5 years; mean DAS28-ESR mm/hour: 3.92 ± 1.34; majority had moderate RA activity.	Exposure to TCZ assessed as a bDMARDs in RA patients; mean duration of use 3.15± 11.90 years; follow-up period 6 months.	tDMARDs: hydroxychloroquine, MTX, sulfasalazine, and leflunomide; bDMARDs: etanercept, adalimumab, golimumab, abatacept, tofacitinib, and rituximab. Oral corticosteroids: 76.6% of the RA population on prednisone; dosage: no information	Main outcome was prevalence of pre-existing depression assessed using the standardised HADS-D; scores 11–21 were considered to have depression; OR of less severe depression 1.21, 95% CI 0.27, 5.35.	9
Baghdadi et al, 2021 [34]	Total RA 271 (females 180, males 91)	Cross-sectional	Saudi Arabia	RA diagnosed according to the revised ACR (1987) or EULAR/ACR 2010 classification criteria; mean age: 51.65 ± 11.71 years; RA duration ≥3 years.	Exposure to TCZ assessed as a DMARDs in RA patients; duration of use ≥8 weeks; no information about dose available; follow-up period 1 year.	Antirheumatic drugs; no available information about the drug names. Oral corticosteroids used and adjusted in the analysis, but no information available about its dose.	Prevalence of depression was the main outcome assessed by the standardised HADS-D; scores 11–21 were considered newly diagnosed depression; RA patients with pre-existing depression or the use of antidepressant medications were excluded; OR 4.16, 95% CI 1.10, 15.79.	10

Baghdadi et al, 2023 [35]	Total RA 213 (females 183, males 30)	Cross-sectional	Saudi Arabia	RA diagnosed according to the revised ACR (1987) or EULAR/ACR 2010 classification criteria; age: majority 51–65 years; RA duration: majority 6–10 years; mean CRP μg/mL: 8.6 ±18.5; mean ESR mm/hour: 41.7 ± 25.6.	Exposure to TCZ assessed as a DMARDs in RA patients; duration of use ≥8 weeks; mean dose: 285.6 ± 194.6 mg, follow-up period 1 year.	Various tDMARDs (MTX, and hydroxychloroquine), and bDMARDs abatacept and adalimumab. Oral corticosteroid used and adjusted in the analysis but no information about its dose.	Prevalence of depression was the main outcome assessed using the standardised HADS-D; scores 11–21 were considered newly diagnosed depression; RA patients with pre-existing depression or use of antidepressants were excluded; β −0.072, 95% CI −0.989, 0.331.	11
Behrens et al, 2022 [36]	Total RA 474 (females 359, males 115)	PCS (the ARA*TA* study; NCT02251860)	Germany	Active RA diagnosed by clinicians' assessment during routine daily care; mean age: 56.0 ± 12.7 years; mean RA duration: 11.2 ± 8.8 years; mean DAS28-ESR mm/hour: 4.9 ± 1.2 (moderate RA activity).	Exposure to TCZ defined as RA patient receiving a first dose of subcutaneous TCZ ≤4 weeks after the baseline visit (study visits at weeks 4, 12, 24, 36, and 52).	Tocilizumab-naive patients: tDMARDs include MTX (oral or parental), leflunomide, cyclosporine A, gold, azathioprine, tofacitinib, and sulfasalazine; bDMARDs, no information about these medications were included. Mean systematic glucocorticoid dose for: mild RA 7.5±5.1 mg/day, moderate RA 7.8 ±7.1 mg/day, and severe RA 7.1 ±3.9 mg/day.	Prevalence of pre-existing depression assessed as a mental health outcome using a validated self-reported questionnaire for depression in RA (BDI-II); scores 20–28 were considered as moderate depression, and ≥29 as severe depression; 4.8% used antidepressant medication; at week 52, 17.7% of patients with moderate depression at baseline improved to no depression (18/39 [46.2%]).	9

(*Continued*)

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Table 1 (Continued).

Reference	N	Study Design	Country	Participants	TCZ monotherapy exposure assessed	Non-TCZ DMARDs and corticosteroids assessed	Depression Outcome	Qi score out of 14
Harrold et al, 2017 [37]	Total RA 255 (females 206, males 49)	PCS	USA	RA diagnosed by rheumatologists and recruited from the Corrona RA registry (NCT01402661); median age (IQR): 61 (49–69) years; median RA duration (IQR): 10 (5–18); RA activity CDAI (IQR): 24.0 (16.7–34.0) suggesting high RA activity.	Exposure to TCZ was defined as TCZ-naive and initiated TCZ as monotherapy between January 1, 2010 and March 31, 2015.	bDMARDs include TNFi and non-TNFi bDMARDs; tDMARDs but no information about the drugs. No information about the use of corticosteroids.	Depression was assessed as one of the 5 domains of the EQ-5D; the prevalence of pre-existing less severe depression among RA patients on TCZ was 47.4%, no patients diagnosed with severe depression; no information on use of antidepressants; after 1 year on TCZ, 20%–36% improvement in depression.	11
Tiosano et al, 2020 [21]	Total RA 91 (females 72, males 19)	PCS	Israel	RA diagnosed according to the revised ACR (1987) or EULAR/ACR 2010 classification criteria; mean age: 55.3 ± 10.9 years; mean RA duration: 7.9 ± 8.9 years; mean RA activity (DAS28): 5.82 ± 1.05 (high RA activity).	Exposure to TCZ defined as a subcutaneous injection of TCZ with a single fixed dose (162 mg for 24 weeks), irrespective of body weight.	tDMARDs: MTX, other tDMARDs; bDMARDs but no information about the drug names. Oral corticosteroids: prednisone or equivalent dose of ≤10 mg/day.	Depression was assessed as one of the outcomes using the HDRS; scores ≥18 were considered to have pre-existing depression; no information about the use of antidepressant medication; after 1 year of TCZ; 25% decrease in HDRS during follow-up (OR 9.70, 95% CI 1.93, 65.38).	9

Rathbun et al, 2016 [41]	Total RA 2551 (females 1280, males 1271)	PCS	USA	RA diagnosed by rheumatologists and recruited from the Corrona RA registry (NCT01402661); mean age: 57.61 ± 12.73 years; mean duration of RA: 10.35 ± 9.79 years; mean RA activity measured by CDAI: 24.67 ± 13.97 (high RA activity).	Exposure to TCZ assessed as a DMARDs in RA patients; no other information available; follow-up at 6 and 12 months.	bDMARDs usage vs RA naive: utilization of any bDMARDs before the index time point, medication type was characterized by 2 groups: TNF and non-TNF; tDMARDs: leflunomide, sulfasalazine, azathioprine, MTX, hydroxychloroquine, minocycline, auranofin, penicillamine, and cyclosporine. Oral corticosteroids: prior prednisone use adjusted in the analysis, but no information available about its dose.	Depression assessed as history of pre-existing depression defined as a self-reported lifetime prevalence at enrolment or presence of depressive symptoms during follow-up before starting TCZ therapy; prevalence of depression among RA patients taking TCZ was 2.41%; 53.26% of them used antidepressants.	11
Matcham et al, 2018 [39]	Total RA 18,421 (females 14,065, males 4356)	PCS	UK	RA diagnosed according to the revised ACR (1987) or EULAR/ACR 2010 classification criteria; mean age: 56.4 ± 12.4 year; mean RA duration: 12.6 ± 9.7 years; mean RA activity (DAS28): 6.4 ± 1.1 (high RA activity).	Exposure to TCZ was assessed as a bDMARDs for good treatment response by 1 year; first exposure to TCZ; no information available about the dose.	bDMARDs: Etanercept, infliximab, adalimumab, rituximab, certolizumab, infliximab biosimilar; first bDMARDs exposure. No information available about the use of corticosteroids.	Depression was identified through reporting a history of depression, SF36 or the EuroQol (EQ5D); RA patients asked history of using antidepressant medications; OR of less severe pre-existing depression 0.80, 95% CI 0.69, 0.92.	11

(*Continued*)

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Table 1 (Continued).

Reference	N	Study Design	Country	Participants	TCZ monotherapy exposure assessed	Non-TCZ DMARDs and corticosteroids assessed	Depression Outcome	Qi score out of 14
Kremer et al, 2011 [38]	Total RA 1,196 (females 989, males 207)	Randomized, double-blind placebo, controlled trial; Phase 3 LITHE trial	13 countries Australia, Brazil, China, Denmark Finland, France, Greece, Italy, Mexico, Poland, South Africa, Spain, USA	RA diagnosed according to revised ACR (1987) classification criteria; median age (IQR): 53 (44–61) years; median RA duration (IQR): 7.3 (3.1–13.5) years; median RA activity (DAS28): 6.5 (high RA activity).	Exposure to TCZ defined as receiving intravenous infusion of 8 mg/kg or 4 mg/kg or every 4 weeks for 52 weeks.	tDMARDs: MTX, dose 10–25 mg/week. Oral corticosteroids: prednisone or equivalent dose of ≤10 mg/day. Patients excluded, if treated with an intra-articular or parenteral corticosteroid ≤6 weeks prior to the baseline visit.	Depression clinically assessed as an adverse event, but no detailed information available; the prevalence of less severe pre-existing depression was 10.1%; 7.4% of them used antidepressants.	14
Burmester et al, 2017 [31]	Total RA 1157 (females 904, males 253)	Randomised, placebo-controlled FUNCTION trial	USA	RA diagnosed according to the revised ACR (1987) classification criteria; median age (IQR): 53 (41–60) years; median RA duration (IQR): 0.2 (0.1–0.6) years; mean RA activity (DAS28): 6.5 (high RA activity).	Exposure to TCZ was defined as receiving an intravenous infusion of monotherapy every 4 weeks: 8 mg/kg (as TCZ + placebo) or combined with tDMARDs: 4 and 8 mg/kg (as TCZ + MTX) for 52 weeks until the end of the double-blind treatment (week 104).	tDMARDs in combination with TCZ: MTX; prescribed as oral capsules starting at 7.5 mg/week to a maximum of 20 mg/week; mean MTX dose at week 52: 17.3 ±4.53 mg/week; mean MTX dose at week 104: 16.2 ± 6.18 mg/week. No information on corticosteroid use (only reported as an adverse effect)	Depression clinically assessed as an adverse event, but no detailed information available; the prevalence of depression was 7.3%; 5.5% used antidepressants.	14

Genovese et al, 2008 [32]	Total RA 1220 (females 165, males 1055)	Randomised, placebo-controlled TOWARD study	19 countries: Australia, Argentina, Brazil, Canada, China, Costa Rica, Bradna, Czech Republic, Denmark Finland, France, Germany Mexico, Panama, Russia, South Africa, Sweden, Thailand, USA	RA diagnosed according to the revised ACR (1987) classification criteria; mean age: 53 ± 13 years; mean RA duration: 9.8 ± 8.8 years; mean RA activity (DAS28): 6.7 ± 1.0 (high RA activity).	Exposure to TCZ monotherapy was defined as receiving an intravenous infusion of 8 mg/kg every 4 weeks (as TCZ + placebo) for 24 weeks.	tDMARDs in combination with TCZ: MTX; RA patients received a stable dose for ≥8 weeks. Oral corticosteroids: prednisone or equivalent dose of ≤10 mg/day.	Depression was clinically assessed as a relevant comorbid condition but no detailed information available; prevalence of less severe pre-existing depression was 10%; 8.6% used antidepressant medication.	13.5
Jones et al, 2010 [33]	Total RA 673 (females 538, males 135)	Randomised, placebo-controlled AMBITION study	USA	RA diagnosed according to the revised ACR (1987) classification criteria; moderate RA for ≥3 months; severe active RA defined by the presence of >6 SJC from a total of 66, >8 TJC from a total of 68, and CRP level >1 mg/dl or ESR >28 mm/h; median age (IQR): 51 (42–59) years; median (IQR) RA duration: 3.1 (0.6–9.4) years; median (IQR) RA activity (DAS28): 6.8 ± 1.0 (high RA activity).	Exposure to TCZ monotherapy was defined as receiving an intravenous infusion of 8 mg/kg every 4 weeks (as TCZ + placebo) for 24 weeks.	tDMARDs: MTX or in combination with TCZ; MTX starting dose 7.5–20 mg/week for 8 weeks followed by TCZ 8 mg/kg. Oral corticosteroids: prednisone or equivalent dose of ≤10 mg/day.	Depression was clinically assessed as one of the adverse events but no detailed information available; the prevalence of less severe pre-existing depression was 9.6%; 7.4% used antidepressants.	13.5

Abbreviations: ACR, American College of Rheumatology; AMBITION, Actemra versus methotrexate double-blind investigative trial in monotherapy; ARA, American Rheumatism Association; ARA*TA*, s a prospective, non-interventional, multicenter, observational study in Germany to evaluate the long-term effectiveness and tolerability of subcutaneously administered tocilizumab in participants with rheumatoid arthritis in daily clinical practice; BDI-II, Beck Depression Inventory II (BDI-II) questionnaire for RA; bDMARDs, biological disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; Corrona, Consortium of Rheumatology Researchers of North America; CRP, C-reactive protein; DAS28, Disease activity score on 28 joints; EQ-5D, the generic quality of life scale; ESR, erythrocyte sedimentation rate; EULAR, American College of Rheumatology/European League Against Rheumatism; HADS-D, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; IQR, interquartile range; MTX, methotrexate; OR, adjusted odds ratio of depression; PCS, prospective cohort study; Qi, quality score; RA, rheumatoid arthritis; SF36, medical outcomes survey 36-item short form; SJC, swollen joints; TCZ, tocilizumab; tDMARDs, traditional disease-modifying antirheumatic drugs; TJC, tender joints; TNFi, tumor necrosis factor inhibitor; TOWARD, tocilizumab in combination with traditional DMARD therapy (MTX); 95% CI, 95% confidence interval; β, beta coefficient of multiple regression analysis.

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depression among patients with RA, depression was clinically assessed as one of the adverse events in four trials.[31–33,38] All the included studies used standard criteria in selecting patients with RA, except three studies.[36,37,41] All included studies reported the use of TCZ and non-TCZ DMARDs and provided details of the drug names except one study.[34] The mean duration of exposure to TCZ ranged from one month[36] to 3 years.[40] TCZ was administered subcutaneously as a fixed dose[15,29] or as an intravenous infusion of 8 mg/kg or 4 mg/kg every 4 weeks.[31–33,38] The use of oral or systematic corticosteroids (prednisone or equivalent) was assessed and adjusted in most studies except three studies.[31,37,39] While not all studies included in the analysis provided details on the duration and dosage of corticosteroid use, it is noteworthy that all studies reporting corticosteroid usage documented the concurrent administration of low doses of corticosteroids (<10 mg).[21,32,33,36]

Risk of Depression and TCZ Monotherapy

All studies that reported the use of TCZ monotherapy were included in the meta-analysis.[21,34–37,39–41] The observed effect size demonstrated a favorable potential effect of TCZ in mitigating the risk of depression among patients with RA. The QE model RR for all included studies was 0.68 (95% CI 0.20, 2.31), signifying a 32% reduction in the depression risk among patients with RA receiving TCZ monotherapy compared to patients with RA who were not administered TCZ (Figure 2). The RE model revealed a comparable result with an RR of 0.26 (95% CI 0.13, 0.53), indicating a 74% decrease in the risk of depression in patients with RA taking TCZ monotherapy compared to patients with RA not receiving TCZ treatment (Figure 3).

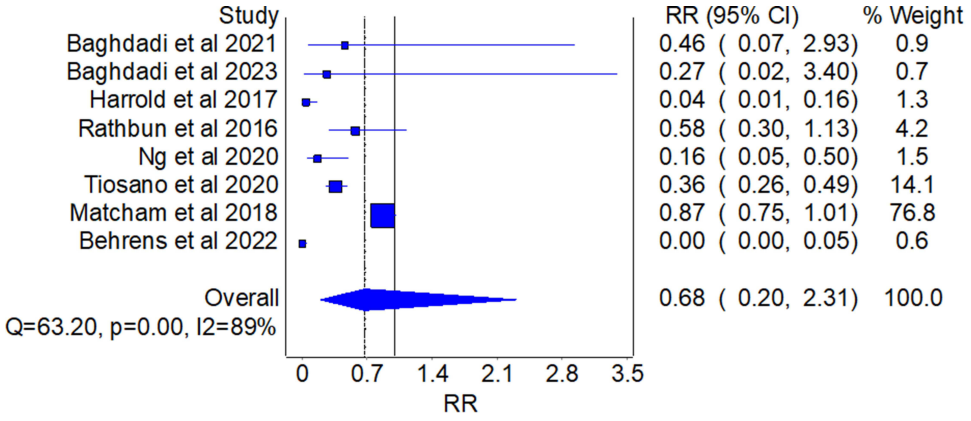

Figure 2 Quality effects model, risk of depression in tocilizumab monotherapy vs non- tocilizumab rheumatoid arthritis patients.
Abbreviations: RR, relative risk.

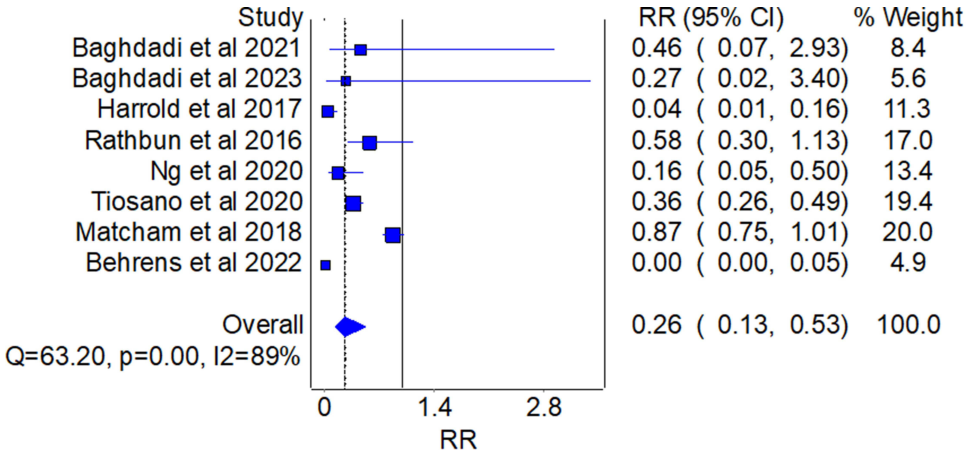

Figure 3 Random effects model, risk of depression in tocilizumab monotherapy vs non-tocilizumab rheumatoid arthritis patients.
Abbreviation: RR, relative risk.

Risk of Depression and TCZ Combination Therapy Vs TCZ Monotherapy

Additional benefits of TCZ combination with MTX therapy compared with TCZ monotherapy in reducing the risk of depression in the RA population were separately examined by including four randomized control trials in the meta-analysis.[31–33,38] The effect size was smaller but still in favor of the beneficial effect of TCZ exposure in reducing the risk of depression in patients with RA. The QE model RR for all these studies was 0.87 (95% CI 0.66, 1.16), implying that the risk of depression in patients with RA exposed to TCZ combined with MTX was reduced by 13% compared to patients with RA taking TCZ monotherapy (Figure 4). The RE model showed a similar result, an RR of 0.86 (95% CI 0.65, 1.13), suggesting there was a 14% reduction in the risk of depression among patients with RA taking combined therapy compared to those on TCZ monotherapy (Figure 5).

Sensitivity Analysis of the Risk of Depression and TCZ Monotherapy

The sensitivity analysis (Table 2) investigated the potential implications of numerous factors that affect depression outcomes and evaluated the extent of susceptibility of the derived findings to such alterations. Factors that could potentially influence depression outcomes were considered in this comprehensive analysis. The pooled RR was recalculated after subgrouping the mean age of patients with RA (≤55 years or >55 years), average disease duration (≤7 years or >7 years), length of follow-up (≤1 year or >1 year), study design (prospective cohort or non-cohort), depression diagnosis (utilizing standardized depression scores or through historical/self-reported data), onset of diagnosing depression (pre-existing or newly diagnosed depression), duration of exposure to TCZ monotherapy (≤1 year or >1 year), assessment of RA disease activity measure by DAS28 or CDAI (conducted or not conducted), level of RA severity (moderate or high RA severity), corticosteroid usage vs non-usage, publication year (before/during 2020 or after 2020), and the geographic location of publication (North America [USA], Middle East, and Europe).

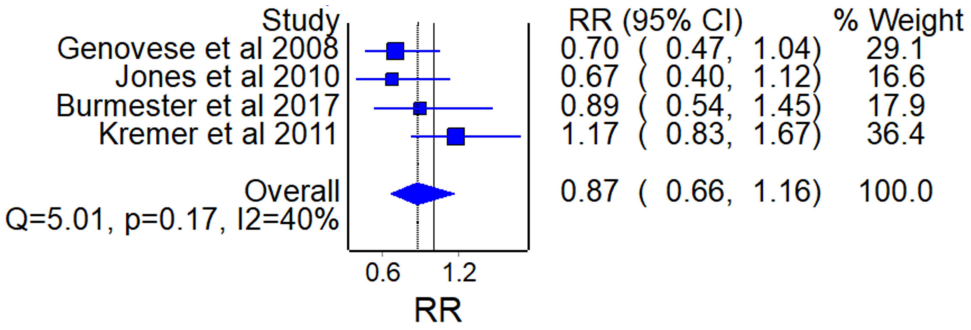

Figure 4 Quality effects model of additional risk reduction of depression in patients with rheumatoid arthritis on tocilizumab combined with methotrexate compared to tocilizumab monotherapy.
Abbreviation: RR, relative risk.

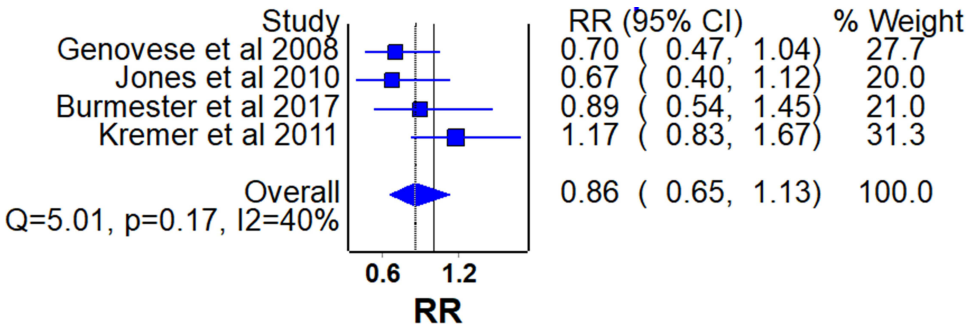

Figure 5 Random effects model of additional risk reduction of depression in rheumatoid arthritis patients on tocilizumab combined with methotrexate compared to tocilizumab monotherapy.

Table 2 Sensitivity Analysis of Depression in Patients with RA on Tocilizumab Monotherapy (N= 9)

Parameters and depression [RR QE model (95% CI)]
Mean age of subjects (years)
≤55 (n = 2): 0.84 (95% CI 0.59, 1.18) >55 (n = 6): 0.68 (95% CI 0.19, 2.37)
Mean duration of RA (years)
≤7 (n = 2): 0.22 (95% CI 0.09, 0.59) >7 (n = 7): 0.57 (95% CI 0.26, 1.23)
Time of follow-up (years)
≤1 (n = 6): 0.72 (95% CI 0.29, 1.77) >1 (n = 3): 0.67 (95% CI 0.01, 6.31)
Study design
Prospective cohort (n=5): 0.69 (95% CI 0.19, 2.44) Non-cohort (n=4): 0.73 (95% CI 0.18, 3.01)
Diagnosis of depression
Standardized depression score (n = 6): 0.24 (95% CI 0.05, 1.20) History or self-reported: (n = 3): 0.84 (95% CI 0.73, 0.96)
Onset of diagnosis of depression
Pre-existing depression (n=6): 0.67 (95% CI 0.19, 2.41) Newly diagnosed depression (n=2): 0.38 (95% CI 0.08, 1.68)
Duration of exposure to TCZ monotherapy (years)
<1 (n = 3): 0.14 (95% CI 0.01, 2.77) ≥1 (n = 6): 0.63 (95% CI 0.31, 1.28)
RA disease activity measurement by DAS28 or CDAI
Measured (n=6): 0.56 (95% CI 0.32, 0.96) Not measured (n=2): 1.54 (95% CI 0.44, 5.47)
Level of RA severity
Moderate RA severity (n=2): 0.09 (95% CI 1.1, 8.28) High RA severity (n=4): 0.71 (95% CI 0.24, 2.41)
Use of corticosteroids
Corticosteroids used (n = 6): 0.91 (95% CI 0.39, 2.08) Corticosteroids not used (n = 3): 0.71 (95% CI 0.20, 2.54)
Year of publication
≤2020 (n = 4): 0.72 (95% CI 0.36, 1.44) >2020 (n = 5): 0.27 (95% CI 0.06, 1.17)
*Country of publication
North America (USA) (n = 3): 0.35 (95% CI 0.02, 6.79) Middle East (n =3): 0.67 (95% CI 0.18, 2.53) Europe (n = 2): 0.74 (95% CI 0.41, 1.33)

Notes: *one study from Taiwan was excluded because it was the only Asian country.
Abbreviations: CI, confidence interval; n, number of studies involved in the analysis; DAS28, rheumatoid arthritis disease activity; QE, quality-effects model; RA, rheumatoid arthritis; RR, relative risk; TCZ, tocilizumab.

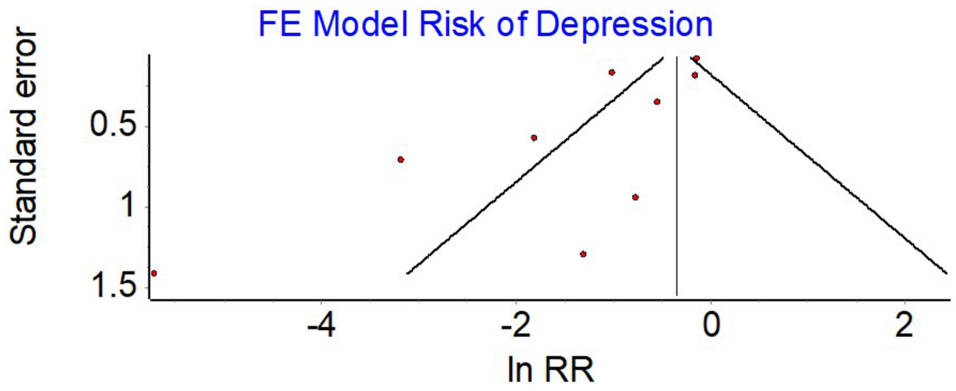

Figure 6 Funnel plot.
Abbreviation: RR, relative risk.

Table 2 shows that patients with RA on TCZ monotherapy had greater reduction in the risk for development of depression, if they were older (>55 years), the RA duration was shorter (≤7 years), follow-up time was longer (>1 years), study design was a prospective cohort, diagnosis of depression was based on a standardized criteria, newly diagnosed depression, duration of TCZ exposure was shorter (<1 year), RA disease activity was measured and adjusted in the study, moderate RA severity, corticosteroids were not used, and the studies were published after 2020.

Subgrouping results of the studies based on different regions revealed that the risk of depression in TCZ users decreased to a greater extent in North American patients recruited for studies as opposed to those from Europe and the Middle East. The funnel plot represents the 12 studies included in the analysis (Figure 6). Ideally, symmetry would suggest the absence of publication bias. However, the plot displays some asymmetry, indicating potential publication bias. This observation is supported by the results of the Egger's test, which shows significant asymmetry ($p<0.05$).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to study the effect of TCZ on depression among the RA population. The findings present substantial evidence, revealing a noteworthy positive influence of this bDMARDs in reducing the risk of developing depression in patients with RA (RR 0.68, 95% CI 0.20, 2.31). The effect size was in favor of the beneficial effect of TCZ exposure reducing the risk of depression in patients with RA, even when TCZ was combined with MTX, despite a slight increase in the risk of depression (RR 0.87, 95% CI 066, 1.16).

Often observed as a prevalent accompanying condition, depression tends to intertwine itself with RA, significantly affecting the lives of patients and their families.[43] In Saudi Arabia, comprehensive data regarding the burden of RA remains scarce. In an effort to address this issue, the Saudi Society for Rheumatology established the Saudi Arthritis Registry in 2018. Although it is a national, prospective, longitudinal database, no information from this registry has been published as yet.[44] A 1998 study approximated the prevalence of RA at 2.2 per 1,000 individuals in the Qassim region of Saudi Arabia.[45] Recently, an observational investigation within the nation demonstrated that patients with RA were four times more likely to develop depression in comparison to patients diagnosed with other chronic illnesses encountered in primary healthcare settings.[34]

To date, there is substantial evidence that the use of TNFi reduces the incident rate of depression in rheumatic diseases.[8] Infliximab was studied as an antidepressant for treatment-resistant depression. A systematic review and meta-analysis of six trials explored the effects of TNFi medication on depression outcomes for chronic physical conditions.[7] However, some studies have shown contradictory results where treatment with TCZ did not have a unique or superior effect on depressive symptoms compared to treatment with other bDMARDs. This result could be biased and affected by the presence of comorbidities, treatment population (ie severely medically ill), baseline measures used, study design,[46] and RA disease activity.[47] It is important to note that current evidence for the effect of TCZ on depression is still limited,

and more studies are required to fully understand its potential. However, our preliminary findings indicate that TCZ could represent a novel therapeutic option for managing both, RA and associated depression symptoms.

In line with the findings of this meta-analysis, TCZ was effective in reducing depressive symptoms mitigating RA-related inflammation. Patients treated with TCZ showed a substantial decrease in clinical and self-reported measures of depression compared to those receiving the TNFi adalimumab.[48] These findings highlighted that this improvement may be due to the reduced IL-6 levels, suggesting a possibly favorable role for TCZ in managing comorbid depression. Similarly, a study on a cohort of 117 Japanese patients with RA and found that the effect of TCZ on depressive symptoms was comparable to that of other bDMARDs, such as infliximab and adalimumab.[49] They reported that while depression scores improved substantially after six months of treatment with TCZ, no significant difference was observed in the group treated with other bDMARDs.

Another study explored the effect of TCZ on depression in comparison to TNFi and found that patients treated with TCZ exhibited a substantial improvement in depression scores (assessed by the Patient Health Questionnaire-9) compared to those treated with TNFi ($p < 0.05$).[50] This suggests TCZ may have superior efficacy in reducing depressive symptoms among patients with RA. Matcham et al (2017)[39] investigated the effects of different bDMARDs, including TCZ, on the emotional well-being and mood disorders of patients with RA. The results revealed IL-6 inhibition through TCZ was associated with better mental health outcomes compared to other bDMARDs, such as TNFi and abatacept (inhibitor of T cell co-stimulation).

The effect size in our meta-analysis was still in favor of the beneficial effect of TCZ exposure in reducing the risk of depression in patients with RA, even when TCZ was combined with MTX, despite the slight increase in the risk of depression, there was 32% and 13% reduction in the risk of depression among patients with RA on TCZ monotherapy vs combined therapy, respectively. A recent study compared the effects of monotherapy and combined bDMARDs and tDMARDs on patients' depression, anxiety, and quality of life and found that neither monotherapy nor combined DMARDs showed superiority over each other in terms of their effects on anxiety and depression in patients with RA.[51] Another study of several DMARDs with various mechanisms of action assessed the most effective DMARD for treating RA and improving mental health.[52] However, it found no major differences between the treatments. The highest effect on mental health was seen with treatments targeting IL-6, and anti-TNF therapies had the weakest effect; this evidence supports the beneficial effects of TCZ for reducing the risk of depression, as it is a bDMARD that targets IL-6.

Recently, numerous investigations have concentrated on the character of the association between inflammatory disorders and psychiatric comorbidity, specifically anxiety and depression.[53–55] Emerging evidence indicates a connection between the inflammatory pathways in RA and depression. Notably, inflammatory cytokines such as TNF-α and IL-6 can be present at higher levels in individuals with depressive disorders.[6] Recent findings suggest that RA treatments targeting TNF-α inhibitors may enhance mental health outcomes for depressed patients with high inflammation levels[8] and those with chronic physical illnesses.[7] It has been posited that IL-6 may serve as a crucial component in mediating this connection. Reduced serum concentrations of IL-6 have been linked to a robust reaction to stress-inducing occurrences, while heightened levels have been associated with depressive moods. Genetic variations in the IL-6 gene and the dysregulation of the hypothalamic-pituitary-adrenal axis due to increased levels of IL-6 have been postulated as potential pathways through which this cytokine exerts its neuropsychiatric effects.[19] In terms of IL-6 antagonism effects, a treatment plan involving TCZ has shown positive effects on mental health among patients with RA, resulting in higher BDI-II scores compared to the placebo and adalimumab, a TNFi.[56,57] An evaluation of depression levels utilizing the Health Assessment Questionnaire and generic quality of life (EQ-5D) scales[37] showed 33% of the RA patient group experienced improved psychiatric symptoms with TCZ treatment. Therefore, TCZ effectively inhibits the classic and trans-signaling pathways of IL-6, which are responsible for the majority of its inflammatory effects; thus, making it the preferred therapeutic agent for comprehensive IL-6 inhibition.[58]

Potential factors that could influence the pooled results were studied in the subgroup analysis. A relatively lower risk of depression was observed in patients aged >55 years (RR 0.68) compared to those ≤55 years of age (RR 0.84). It was reported that most patients aged 55–59 years had been commenced on at least one of the bDMARDs[59] and the reduction in the risk of depression could be explained by the duration of exposure to TCZ. This meta-analysis also found that the risk of depression was reduced among patients with RA with a TCZ exposure of <1 year and among patients with

a shorter duration of RA (≤7 years). This is similar to the finding by a randomized trial, where the maximum efficacy of TCZ was recorded two weeks after infusion. This active interventional double-blind, randomized controlled trial with a placebo study examined the behavioral and cognitive outcomes of TCZ administration for individuals diagnosed with depression and high C-reactive protein levels.[20] This ongoing trial will help researchers determine whether the inhibition of the IL-6 pathway using TCZ affects the somatic symptom scores of depressed patients around day 14 post-infusion.

Our finding of a lower risk of developing depression among patients with a shorter RA duration could also be explained by the RA activity status. Studies that considered the DAS28 or CDAI of their population showed a lower risk of depression, while studies that did not measure the level of disease activity had a higher risk of depression (RR 0.56, 95% CI 0.32, 0.96 vs 1.54, 95% CI 0.44, 5.47). A higher risk of depression was also found among RA patients who had high RA severity (RR 0.71, 95% CI 0.24, 2.41) with pre-existing depression (RR 0.67, 95% CI 0.19, 2.41). A longer duration of RA was statistically significant in the effectiveness of TCZ used to treat biologic-naive patients with established RA. The increase in disease duration resulted in a 9% decrease in the rate of achieving an ACR50 response, and each additional 5-year period of RA duration lowered the probability of attaining CDAI remission by 15%[60] Patients with active, treatment-resistant RA who commenced TCZ monotherapy demonstrated significant enhancements in comprehensive disease activity indices and patient-reported outcomes at the one-year mark, irrespective of prior TNFi exposure.[37] Thus, RA activity and duration, alone or in combination with other baseline features, affected the outcomes of TCZ.

Another explanation of the observed higher risk of depression among patients with higher disease activity could be that patients with RA may have been commenced on corticosteroids to reach remission. In our meta-analysis, studies where patients used corticosteroids showed a smaller reduction in the depression risk compared to studies with no history of using corticosteroids in the RA population (RR 0.91, 95% CI 0.39, 2.08 vs RR 0.71, 95% CI 0.20, 2.54). Although RA patients in these studies received a low dose of corticosteroids (<10 mg), and such use was adjusted in the regression model to eliminate its confounding effect, there could be a residual effect, which may explain a reduction in the risk of depression, less than that observed in studies without corticosteroid use. There is evidence that frequent utilization of systemic corticosteroids has been linked to diminished executive cognitive performance and an elevated probability of mood and anxiety disorders within the general adult population.[61] However, there is lack of evidence about such an effect on depression or in the RA population.[62]

This meta-analysis found further reduction in the risk of depression, if the diagnosis of depression was based on standardized criteria (RR 0.69, 95% CI 0.19, 2.44) and examined in longitudinal prospective cohort studies (RR 0.24, 95% CI 0.05, 1.20) with a longer follow-up period (RR 0.67, 95% CI 0.01, 6.31) (Table 2). It could be due to the latency period of depression[63] and exposure to severe or chronic stress induced by RA,[64] and bidirectional association between RA and depression.[65] Patients with RA had a 47% higher risk of developing depression compared to the control group.[4] Similarly, those who had depression showed a 34% greater risk of being diagnosed with RA.

The risk of depression among TCZ users was further reduced in patients recruited for studies conducted in North America (USA) as opposed to patients recruited for studies in Europe and the Middle East. Determining the precise origin of these nation-specific discrepancies remains a challenging task due to mental healthcare disparities[66] and possible variations in the social determinants of health influenced by geography, epidemiology of chronic diseases (including depression), measurement methodologies, sample techniques, cultural idiosyncrasies, and types of lifestyles.[67] Recent research has indicated the influence of latitudinal variation of factors, including geographical localization, geomagnetic alignment, and developmental status, which may ultimately affect the age of onset for RA.[68] In the Middle Eastern region, a study reported 67.5% of patients with RA exhibited moderate to severe depression.[68] This proportion is strikingly similar to the 66% reported by Rezaei et al in their study in Egypt.[69] This figure surpasses the percentages of depression reported in two Egyptian studies, 15%[70] and 45%,[71] respectively, although it falls short of the 80% depression reported by another study.[72] Other discrepancies can be observed when compared to prevalence rates in different nations — 2% in Morocco, 4% in Canada, 33% in the US,[73] and 45% in Tunis.[74] The discrepancies observed among various studies, particularly those involving Egyptian patients with RA can potentially be ascribed to the utilization of diverse measurement instruments and varying levels of disease activity. However, pinpointing the exact cause of these country-specific disparities, whether from distinct measurement approaches, sample sizes or cultural nuances, remains a challenging endeavor.

Another factor that could affect the true effects of TCZ in reducing the risk of depression in RA is its high cost.[75] It was estimated that biologics can cost $1,200–1,400 per month ($14,400–16,800 per year).[76] In comparison to MTX therapy, the overall costs and quality-adjusted life years associated with TCZ treatment were observed to be approximately 1.5 times and 1.3 times greater, respectively.[77] Given its high cost, TCZ is not affordable in several geographic locations, including rural and developing countries.[78] In many countries, including Saudi Arabia, health insurance may not cover the expenses of TCZ or patients with RA may not have health insurance as private healthcare insurance is a mandatory requirement only for expats, Saudi nationals employed in the private sector, and their dependents.[79] The availability of biosimilars of TCZ for RA signifies a significant advancement in biopharmaceuticals, providing patients with alternative treatment options that offer comparable efficacy and safety to the reference biologic medication.[80] Biosimilars of TCZ, which are biological products that exhibit a high degree of structural similarity and functional equivalence to the officially approved reference product (TCZ) offer a promising avenue for enhancing treatment accessibility.[81] The utilization of biosimilars has the potential to generate cost savings, provided they are priced judiciously and are supported by payers and healthcare authorities, while also being accepted by patients. Regulatory bodies provide comprehensive guidance on the requisite evidence for establishing similarity between a biosimilar and its reference biologic.[82] Key criteria include demonstrating no clinically significant disparities in terms of molecular structure, purity, pharmacokinetics, pharmacodynamics, safety, immunogenicity, and efficacy compared to the reference product, with supporting data derived from rigorous clinical investigations.

In addition to the financial burden of TCZ, it is usually administered as an infusion, which needs hospital care. Many patients with RA may not have access to healthcare facilities as many public hospitals are overloaded and many patients may not have private health insurance to cover the expenses of their treatment.[82] Although healthcare in Saudi Arabia is free, privatization and health insurance policies have been introduced recently, which may affect the coverage of drug expenses and access to healthcare.[82] The availability of TCZ in subcutaneous form represents a notable advancement in healthcare delivery, as it reduces the necessity for hospital visits and consequently diminishes the overall cost of administration.[83] This alternative route of administration offers patients a convenient and potentially more cost-effective option for receiving TCZ therapy, thereby enhancing treatment accessibility and potentially improving patient compliance. The shift toward subcutaneous administration of TCZ aligns with the broader trend in healthcare toward more patient-centered and cost-efficient care delivery models.

This systematic review and meta-analysis has numerous strengths. The Qi score (quality) of the studies was calculated and included in the effect estimate calculation. Another strength of this meta-analysis is that many factors which may influence the effectiveness of TCZ on reducing the risk of depression among patients with RA such as the age of the patients, RA duration, duration of exposure to TCZ etc. were considered. The effects of these factors, which may act as confounders influencing the effect estimates, were additionally explored through subgroup analyses that remained consistent with a decreased depression risk among patients with RA exposed to TCZ.

However, this study also has some limitations. One of them is the lack of control over corticosteroid exposure. Although a few patients with RA have been given small doses of prednisolone (≤10 mg/day) at some point, there is no detailed information about its duration. The RA duration of a patient is a key factor when it comes to the use of corticosteroids in RA management. The ACR recommends starting RA treatment with corticosteroids, especially in early RA, based on the 2015 ACR and 2019 EULAR guidelines. Patients with early RA are usually prescribed low doses of corticosteroids (≤10 mg of prednisolone or its equivalent). The ACR identifies early RA as a disease with a duration of ≤6 months.[82,84] However, in this meta-analysis most of the patients with RA were diagnosed with established RA as the RA duration ranged between 3 and 12 years. The sensitivity analysis showed that the risk of depression was reduced among patients who had a shorter duration of RA (≤7 years). Evaluation of depression presents a multitude of challenges. These challenges include the complex interaction between depression and disease severity, as well as the use of standardized and validated instruments or scales to accurately assess depression levels. Furthermore, obtaining an accurate baseline depression status can be complicated by factors such as pharmacological treatment for depression or the use of sleep therapy that may impact depressive symptoms.[85] Seasonal variability and the potential impact of light exposure on depression must also be considered in the evaluation process.[86] Mental healthcare disparities and socio-cultural aspects also play a significant role in the manifestation and evaluation of depression, further complicating the

assessment of this mental health condition.[66] Addressing these limitations is essential for the development of effective strategies for the prevention and treatment of depression in the RA population.

It was challenging to ascertain the TCZ naïveté of RA patients due to the absence of information in few studies.[34,35,40,41] Our diligent efforts to contact the authors yielded no response. We conducted a subgroup analysis to assess the duration of exposure to TCZ and discovered a reduction in the risk of depression among RA patients with less than one year of TCZ exposure. These findings align with those of a randomized trial, which reported the maximum effectiveness of TCZ two weeks after infusion;[20] additionally, evidence shows that the majority of RA patients discontinue the TCZ in the first year due to adverse effects and events.[87] Although TCZ combined with other tDMARDs is marginally superior to TCZ monotherapy in achieving DAS28 < 2.6 and a better clinical response, this is at the cost of an increased risk of adverse effects.[88] There is evidence of publication bias, as studies with larger sample sizes and positive outcomes are published more often, while those with insignificant or negative results are seldom submitted. Additionally, these findings can be further hindered by reviewers and editors rejecting such papers. The funnel plot of the 12 studies demonstrates asymmetry, which suggests potential bias, further confirmed by Egger's test showing significant asymmetry ($p<0.05$). This indicates that smaller studies might be underrepresented, thereby impacting the overall interpretation of the risk of depression in the meta-analysis. To complicate matters further, each study had varying ages of participants, varied RA durations and follow-ups, different geographic locations (countries), and times when the studies were conducted and results published. However, sensitivity analysis (Table 2) was conducted to assess the robustness of our findings and ensure that our results are not unduly influenced by the effect of these factors on depression.

Conclusion

The findings of our study suggest that TCZ has a beneficial impact on depression in patients with RA. Although the precise mechanisms underlying these effects remain incompletely understood, it is postulated that this bDMARD may alleviate depression by reducing inflammation and correcting immune system dysregulation through its regulation of IL-6. This reduction in systemic inflammation might contribute to improved mood and cognitive function, highlighting an important link between inflammatory pathways and mental health. These findings highlight the need for integrated treatment approaches that address both physical and psychological aspects of chronic diseases like RA.

However, despite these promising findings, further research is warranted to corroborate the observed benefits of TCZ on depression in RA patients. Larger-scale studies with extended follow-up periods are needed to comprehensively evaluate the long-term efficacy and safety profile of TCZ in managing depression in this population. Comparative studies assessing TCZ against other biologic agents are also necessary to ascertain its relative effectiveness and inform treatment pathways decision-making. Investigations into the underlying mechanisms of TCZ's antidepressant effects are essential for a deeper understanding of its therapeutic action. Exploring the possibilities that these beneficial outcomes extend to other inflammatory conditions beyond RA would broaden the clinical implications of TCZ in mental health management. Overall, continued research efforts are imperative to validate and elucidate the potential of TCZ as a therapeutic intervention for depression in patients with RA and potentially other related disorders.

Abbreviations

ACR, American College of Rheumatology; AMBITION, Actemra versus methotrexate double-blind investigative trial in monotherapy; ARA, American Rheumatism Association; BDI-II, Beck Depression Inventory II (BDI-II) questionnaire for RA; bDMARDs, biological disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; Corrona, Consortium of Rheumatology Researchers of North America; CRP, C-reactive protein; DAS28, Disease activity score on 28 joints; EQ-5D, the generic quality of life scale; ESR, erythrocyte sedimentation rate; EULAR, American College of Rheumatology/European League Against Rheumatism; HADS-D, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; IQR, interquartile range; IRR, incidence rate ratio; MTX, methotrexate; OR, adjusted odds ratio of depression; PCS, prospective cohort study; QE, quality effects model; Qi, quality score; RA, rheumatoid arthritis; RE, random effects model; RR, relative risk; SF36, medical outcomes survey 36-item short form; SJC, swollen joints; TCZ, tocilizumab; tDMARDs, traditional disease-modifying antirheumatic drugs; TJC, tender joints; TNFi, tumor

necrosis factor inhibitor; TOWARD, tocilizumab in combination with traditional DMARD therapy (MTX); 95% CI, 95% confidence interval; β, beta coefficient of multiple regression analysis.

Summary

Rheumatoid arthritis is a chronic condition that causes inflammation of joints. It is linked to mental health conditions, including depression. Research suggests that rheumatoid arthritis and depression may share a common inflammatory pathway. New biological anti-inflammatory therapies like tocilizumab used in the treatment of rheumatoid arthritis, may also improve mental health by lowering depression. However, as there is insufficient evidence to support this, the use of tocilizumab in treating depression in patients with rheumatoid arthritis needs to be explored. A systematic review and meta-analysis of previously published studies was conducted to investigate the effect of tocilizumab. Various medical databases were searched and after elimination of duplicates and studies with insufficient information, 12 studies met the criteria for this meta-analysis. The meta-analysis showed that patients with rheumatoid arthritis administered tocilizumab therapy had a lower risk of developing depression compared to those not on this treatment. More controlled trials are required to confirm these positive effects of tocilizumab on depression. If these positive effects are verified by the clinical trials, tocilizumab might have an important implication for patients with rheumatoid arthritis and will positively affect their mental health and quality of life.

Data Sharing Statement

All relevant data are within the manuscript and its supporting information files.

Acknowledgments

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Author Contributions

The author made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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