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REVIEW

Impact of Biological Therapies on Quality of Life in Rheumatoid Arthritis: A Narrative Review

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint damage, pain, and disability, leading to significant impairments in patients' physical, mental, and social well-being. While biological disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, and Janus kinase (JAK) inhibitors have revolutionized the treatment of RA by effectively controlling disease activity, their influence on patients' quality of life (QoL) is crucial but not fully understood. The aim of this review is to evaluate the impact of bDMARDs on QoL in RA patients, particularly focusing on domains such as physical functioning, pain, fatigue, mental health, and social participation. A comprehensive literature search was conducted in databases such as PubMed and the Cochrane Library, including randomized controlled trials, cohort studies, and surveys assessing QoL outcomes in RA patients receiving bDMARD therapy. The review includes studies that utilized the Health Assessment Questionnaire (HAQ), EuroQol-5 Dimension (EQ-5D), and Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Fatigue Severity Scale (FSS), and Patient Global Assessment (PtGA) QoL questionnaires, among others, to assess patient-reported outcomes. The findings of the current review suggest that bDMARDs significantly improve QoL in RA patients by reducing pain, fatigue, and disability while enhancing physical function and mental well-being. However, variability in patient responses, side effects, and the long-term impact of these therapies remain key concerns. Future studies with standardized QoL assessments and longer follow-up periods are needed to provide a more comprehensive understanding of the sustained effects of bDMARD therapy on RA patients' overall well-being.

Keywords: rheumatoid arthritis, biological therapies, QoL, HAQ-DI, patient-reported outcomes, physical function, mental health, fatigue

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovial inflammation, which leads to progressive joint damage, deformity, and functional disability.[1] The pathogenesis of RA involves a complex interplay between genetic susceptibility and environmental factors, leading to immune dysregulation. Key mechanisms include the activation of antigen-presenting cells, autoreactive T and B cells, and the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1).[2,3]

The impact of RA extends beyond joint pathology, significantly impairing patients' physical function and overall QoL. The progressive nature of the disease leads to limitations in daily activities, such as walking and climbing stairs, contributing to reduced independence.[4] Persistent joint pain, fatigue, and stiffness not only limit mobility but also affect mental well-being, increasing the risk of anxiety and depression.[5] Emerging evidence suggests that inflammation itself may contribute to neuropsychiatric symptoms through cytokine-mediated pathways, emphasizing the need for a holistic approach to RA management.[6,7]

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QoL in RA is a multidimensional concept encompassing physical, emotional, and social well-being. It is commonly assessed using validated instruments such as the HAQ, the SF-36, and the EQ-5D.[8] Effective disease management aims to alleviate pain, improve function, and enhance psychosocial health, as these factors collectively influence treatment adherence and patient satisfaction.[9,10] Given the chronic nature of RA, it is essential to consider QoL as an outcome measure in the management of the disease, as it directly correlates with treatment satisfaction, adherence to therapy, and overall health perception.

The advent of biologic disease-modifying antirheumatic drugs (bDMARDs) has transformed RA treatment by targeting specific immune pathways involved in disease progression. TNF inhibitors, IL-6 receptor antagonists, and JAK inhibitors have demonstrated significant efficacy in reducing inflammation, preventing structural damage, and improving functional outcomes.[11,12] However, while these therapies effectively control disease activity, their impact on QoL varies among patients due to factors such as treatment response, comorbidities, and socioeconomic status.[13] Several studies indicate that bDMARDs not only improve physical function but also contribute to better mental health outcomes by reducing pain and fatigue. According to the European League Against Rheumatism (EULAR) 2022 update, biological disease-modifying antirheumatic drugs (bDMARDs) are recommended for patients with rheumatoid arthritis (RA) who have an inadequate response to conventional synthetic DMARDs (csDMARDs) and present poor prognostic factors. In such cases, adding any bDMARD to the csDMARD regimen is advised.[14] Regarding utilization rates, a study analyzing US outpatient data from 2018 to 2022 found that approximately 31.7% of RA patients were treated with bDMARDs.[15] These sources provide evidence for the recommendation of bDMARDs following inadequate response to csDMARDs and indicate that their utilization among RA patients is around 30%, highlighting the adherence to treatment guidelines in clinical practice.

Despite their proven efficacy in disease control, the impact on QoL remains heterogeneous across different patient populations, necessitating further investigation.

Quality of Life as a Key Outcome in Rheumatoid Arthritis

QoL in the context of RA refers to a multifaceted concept encompassing patients' physical, emotional, and social well-being. The physical aspect of QoL in RA patients is closely tied to disease activity, joint damage, and functional disability. Chronic pain, fatigue, joint stiffness, and loss of mobility are some of the most debilitating symptoms that directly influence physical functioning.[16,17] As RA progresses, joint deformities and decreased range of motion may further limit the ability to perform daily activities such as walking, dressing, or cooking. The severity of pain and the degree of physical disability are often quantified using scales like the Disease Activity Score (DAS28) and Visual Analog Scale (VAS), which assess physical functioning and disease burden.[18–20] Although tools assess tools that assess aspects of QoL related to physical function and mental health, including Health Assessment Questionnaire – Disability Index (HAQ-DI) that evaluates functional disability and is frequently used in RA clinical trials; Patient-Reported Outcomes Measurement Information System (PROMIS) which covers multiple domains such as pain, fatigue, depression, and physical function; Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F) which measures fatigue impact in RA patients.[21,22] Biological therapies, particularly in the treatment of autoimmune and chronic inflammatory diseases, have become a cornerstone of clinical management, significantly improving patients' QoL. Numerous studies have demonstrated that biological therapies can positively affect various QoL domains, including physical functioning, emotional well-being, social participation, and productivity.[23–25] In a cohort study by Ines et al reported an improvement of FACIT-F score by 15.06% after sixth month of treatment with biologics.[26] A Similar result was reported in a multi-ethnic cohort of rheumatoid arthritis patients.[27] Biologics, particularly TNF inhibitors (Etanercept, Infliximab, and Adalimumab) and Rituximab, have been shown to effectively reduce fatigue in RA patients. A systematic review by Almeida et al highlights that improvements in fatigue often occur before significant changes in clinical disease activity, suggesting that biologics may target fatigue through mechanisms that go beyond inflammation reduction. This finding aligns with the hypothesis that fatigue in RA is not solely an inflammatory symptom but may involve additional pathways, such as neuroimmune interactions, psychological factors, and central sensitization.[28] One of the key takeaways from this review is the suggestion that fatigue reduction may not be entirely linked to improvements in disease activity. This is particularly important because fatigue is a chronic, multidimensional symptom that significantly impacts patients'

QoL, irrespective of visible joint inflammation. The potential mechanisms by which biologics reduce fatigue include immune modulation, central nervous system effects, and the restoration of circadian rhythm—areas that warrant further exploration. Bessette et al demonstrated statistically significant improvements of HAQ-DI from baseline in patients with moderate to severely active RA treated with abatacept.[29]

A cross-sectional, non-interventional study by Inotai and colleagues reported that RA patients treated with biological agents experience lower disease activity and improved health-related quality of life compared to those receiving non-biological treatments. These findings underscore the importance of considering patient-reported outcomes and utility measures when evaluating treatment effectiveness in RA.[30] These results support the integration of biological therapies into RA treatment regimens to enhance patient well-being. However, the study also highlights the need for individualized treatment plans, as the benefits of biological agents must be weighed against factors such as cost and potential adverse effects.

One of the most direct impacts of biological therapies on QoL is through significant improvements in physical functioning. In RA, joint pain and stiffness are prevalent, causing major limitations in daily activities and physical mobility.[31,32] Numerous studies have demonstrated that patients treated with biological therapies, particularly TNF inhibitors, experienced substantial alleviation of joint pain and stiffness, resulting in improved physical functioning.[33–35] HAQ-DI scores, which is a widely used measure of functional disability. Similarly, pain reduction was commonly reported by patients, leading to a higher degree of physical independence and improved performance of daily tasks. This reduction in physical limitations allows individuals to engage in more physical activity, contributing to better overall health and well-being.[4,24,25]

Chronic inflammatory diseases often lead to psychological distress, including anxiety, depression, and stress, particularly due to persistent symptoms and uncertain disease progression. The improvement in disease control facilitated by biological therapies can have a profound impact on emotional well-being.[36,37] Several observed that, alongside improvements in physical symptoms, patients on biological treatments reported a reduction in depressive symptoms and anxiety. This aligns with findings from other studies, such as those by[38–40] which show that controlling disease activity in RA not only alleviates physical symptoms but also improves mood and overall mental health. Biological treatments seem to reduce the emotional burden of living with a chronic disease, leading to greater psychological resilience and a more optimistic outlook on life. Chronic inflammatory diseases can significantly impair patients' ability to engage in social activities and maintain personal relationships, crucial aspects of quality of life. Biological therapies, particularly anti-TNF agents, have been shown to alleviate these challenges. A study on patients with chronic inflammatory arthritis undergoing biological therapy found that social support from family, friends, and colleagues was essential in influencing a good treatment response. Regular conversations and social interactions were highlighted as important components of this support.[41] Furthermore, the improved QoL associated with biologic therapy can increase productivity and reduce the societal impact of rheumatoid arthritis. Earlier access to biologics for RA patients has been shown to have a positive effect on employment status, indicating enhanced social participation and engagement.[42] These findings suggest that by reducing disease activity and improving physical function, biological therapies enable patients to re-engage in social activities and relationships that were previously hindered by their condition. This restoration of social participation contributes to a better sense of belonging, social satisfaction, and overall mental health, as it fosters a sense of community and reduces isolation.

Chronic diseases significantly impact work-related outcomes, including absenteeism and productivity.[43,44] Biological therapies have been shown to facilitate a return to work and enhance productivity. A study on patients with RA treated with etanercept reported significant reductions in work-related absenteeism and improvements in productivity.[45] Shim et al reported significant improvements of work productivity patients with axial spondyloarthritis undergoing biological therapy.[46] These improvements in work capacity contribute not only to financial stability but also to a sense of personal achievement and identity, which are important aspects of QoL. However, we could not find studies on the relationship between work productivity and biological therapies in the case of rheumatoid arthritis. Further studies are needed for standardized, RA-specific work productivity assessment tools would be valuable.

Biological therapies have been shown to significantly enhance QoL in patients with chronic inflammatory diseases, particularly RA. These improvements encompass various domains, including physical functioning, pain intensity, fatigue, and sleep quality. Fatigue is a prevalent and debilitating symptom in autoimmune diseases. Studies have demonstrated

that biological therapies can lead to notable reductions in fatigue levels. A Cochrane review reported that treatment with biologics resulted in small to moderate reductions in patient-reported fatigue compared to placebo.[28] Improved sleep quality is closely associated with reduced disease activity and pain relief. Research indicates that patients with RA often experience poor sleep quality, which correlates with higher disease activity and pain levels. Effective management of RA through biological therapies has been linked to improvements in sleep quality.[47]

The reduction in disease activity, as measured by indices like the DAS28 in RA, has been directly correlated with improved QoL outcomes. Lower DAS28 scores, indicating reduced disease activity, are associated with better physical function, less pain, and overall enhanced QoL.[11,42] The Table 1 captures the diverse range of study designs, biologic therapies, and outcome measures used to assess the impact of these therapies on quality of life in patients with RA. The QoL improvements outline the various QoL assessment tools used in the studies. Commonly used tools include HAQ-DI, SF-36, FACIT-F, PtGA, EQ-5D, FSS, and others like WPAI-RA.[23–26,28,30,31,38,40,45–69] These tools measure different aspects of patients' health, including physical function, fatigue, and overall well-being.

Factors Influencing Quality of Life Outcomes in Rheumatoid Arthritis

Disease Activity and Treatment Response

The level of RA disease control directly correlates with QoL outcomes. Studies consistently demonstrate that achieving low disease activity or remission improves physical function, reduces pain, and enhances mental health. The ACR and EULAR criteria for treatment response underscore the importance of early and sustained control of disease activity for optimal QoL benefits.[70] Biologic therapies such as adalimumab, infliximab, and etanercept are associated with significant reductions in disease activity and improved patient-reported outcomes.[11,45] Patients who achieve remission often report enhanced physical functioning and reduced fatigue, contributing to better overall QoL. Conversely, inadequate treatment response, marked by persistent joint inflammation and pain, correlates with poorer QoL scores.[36] These findings highlight the necessity of personalized treatment strategies to optimize disease control and QoL outcomes.

A treat-to-target (T2T) strategy, which involves regular monitoring and therapy adjustments to achieve predefined disease activity goals, has been widely endorsed to improve clinical outcomes. A systematic review and meta-regression analysis reported that patients managed with a T2T approach experience higher rates of remission, better physical function, and lower healthcare costs compared to conventional treatment strategies.[71]

Patient Characteristics

Demographic and clinical characteristics significantly influence QoL in RA patients. Age, disease duration, baseline disease severity, and comorbidities play pivotal roles. Older patients often report lower QoL scores due to age-related functional limitations and increased comorbidities, such as cardiovascular diseases and depression.[72] Additionally, longer disease duration correlates with accumulated joint damage and reduced functional capacity, further impacting QoL.[73] Patients with high baseline disease activity tend to exhibit greater improvements in QoL when achieving disease control through biologics, but they may also have a higher burden of initial symptoms. Addressing comorbidities through integrated care is crucial, as these conditions exacerbate pain, disability, and psychological distress, all of which negatively influence QoL.

Adverse Drug Events of Biological Therapies

Although biologic therapies improve disease activity and QoL, their adverse effects may offset these benefits for some patients.[74] Common adverse drug reactions include injection site reactions, increased infection risk, and gastrointestinal disturbances, which may contribute to treatment discontinuation.[13,75] Serious infections associated with TNF inhibitors are a critical concern, particularly in patients with pre-existing risk factors.[76] Patient-reported outcome measures (PROMs) reveal that side effects like fatigue, nausea, and anxiety due to medication concerns can significantly reduce QoL despite clinical improvements in RA symptoms.[24,25,52] Strategies to minimize adverse effects, such as careful patient selection, regular monitoring, and patient education, are essential to maximizing QoL benefits.

Table 1 Summary of Studies Assessing QoL in RA Patients Receiving Biologic Therapy

Study (Year)	Study Design	Sample Size	Biologic Therapy	QoL Measures Used	Main Findings	Key Limitations
Bergman et al (2023)[24]	Phase 3 RCT	N=612	bDMARD-IR patients switched to Upadacitinib (15mg QD) or Abatacept	PROMIS Fatigue, SF-36, FACIT-F, Pain NRS, HAQ-DI	Upadacitinib led to greater improvements in pain, fatigue, and physical function at weeks 12 and 24 vs Abatacept.	Short follow-up, long-term safety not assessed, patient-reported bias.
Bingham et al (2021)[23]	Post hoc analysis of Phase 3 RCTs	N = 1900 (patients with active RA)	Filgotinib (100 mg or 200 mg) vs MTX, Adalimumab, or Placebo in MTX-naïve, MTX-IR, and bDMARD-IR RA patients	HAQ-DI, SF-36 (PCS/MCS), FACIT-Fatigue, WPAI-RA, PtGA	Filgotinib (200 mg) led to the greatest improvements in HAQ-DI, SF-36, and fatigue across all subgroups.	Post hoc nature, heterogeneity of patient subgroups, limited long-term data.
Burmester et al (2023)[48]	Pooled safety analysis	N=3209	Upadacitinib across RA, PsA, AS, AD	General safety outcomes	QoL indirectly assessed; safety outcomes suggest good tolerability across diseases	Safety outcomes vary across indications, limiting direct comparison
Burmester et al (2023)[49]	Randomized Controlled Trial (RCT)	N=1162	Tocilizumab + MTX vs MTX monotherapy	HAQ-DI, SF-36	Tocilizumab significantly improved physical function and QoL in early RA	Early RA population only; results may not generalize to established RA
Cohen et al (2023)[50]	Integrated Analysis	N=4400 (across multiple SELECT trials)	Upadacitinib (15mg/ 30mg) vs Placebo, MTX	General safety outcomes	Upadacitinib showed acceptable safety with higher rates of infections, herpes zoster, and non-melanoma skin cancer (compared to MTX/pacebo)	Safety outcomes primarily focused on adverse events; no QoL-specific outcomes measured.
Combe et al (2023)[51]	Network meta-regression of individual patient data (N = 2 RCTs)	N = 1171 (across two RCTs)	CT-P13 (subcutaneous) vs Infliximab (intravenous)	Not directly reported	CT-P13 (subcutaneous) and intravenous infliximab were found to have comparable efficacy in reducing RA disease activity (DAS28), with no significant difference in clinical outcomes.	Limited data on QoL and long-term outcomes; outcomes only assessed at early and mid-term time points.
Fleischmann et al (2023)[52]	Randomized controlled trial	N = 1000+	Upadacitinib + methotrexate vs Adalimumab + methotrexate	HAQ-DI, SF-36, PtGA	Upadacitinib demonstrated superior efficacy in improving HAQ-DI compared to adalimumab, with a greater proportion of patients achieving low disease activity.	Limited duration of follow-up (48 weeks); does not assess long-term effects beyond 1 year.
Fleischmann et al (2023)[31]	Randomized controlled trial	N = 1300	Upadacitinib (15 mg) + Methotrexate (MTX) vs Adalimumab (40 mg) + MTX	HAQ-DI, SF-36, PtGA	Upadacitinib showed sustained superiority in improving HAQ-DI compared to adalimumab over 3 years.	Short-term safety data for rare adverse events; long-term outcomes beyond 3 years were not evaluated.
Genovese et al (2020)[39]	Randomized controlled trial	N = 1210 (patients with moderate to severe RA refractory to DMARDs)	Filgotinib (200 mg or 100 mg) vs Placebo	HAQ-DI, PtGA, SF-36, FACIT-Fatigue	Filgotinib significantly improved HAQ-DI, and PtGA compared to placebo. Filgotinib was also associated with significant improvements in fatigue and work productivity. Patients on filgotinib had better quality of life as indicated by HAQ-DI and SF-36 scores.	Study duration (24 weeks) may not capture long-term efficacy and safety.

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Table 1 (Continued).

Study (Year)	Study Design	Sample Size	Biologic Therapy	QoL Measures Used	Main Findings	Key Limitations
Genovese et al (2017)[53]	Randomized controlled trial	N = 1305 (patients with moderate to severe RA refractory to DMARD therapy)	Baricitinib (2 mg or 4 mg) vs Placebo	HAQ-DI, PtGA	Baricitinib significantly improved HAQ-DI, PtGA, and other patient-reported outcomes compared to placebo.	The study duration (12 weeks) might not fully capture the long-term safety and efficacy of baricitinib.
Genovese et al (2018)[54]	Randomized controlled trial (RCT)	N = 1197 (patients with RA and inadequate response to MTX)	Sarilumab (150 mg or 200 mg) vs Placebo	HAQ-DI, VAS, PtGA	Sarilumab significantly improved RA disease activity, HAQ-DI, and pain scores compared to placebo.	Study duration (2 years) was relatively long, but the long-term safety and tolerability of sarilumab in patients with comorbidities were not fully explored.
Genovese et al (2021)[55]	Randomized controlled trial (RCT)	N = 494 (patients with RA who were on adalimumab)	Switch from Adalimumab to Tofacitinib (5 mg, twice daily)	HAQ-DI, PtGA	Switching from adalimumab to tofacitinib resulted in similar or improved clinical outcomes for RA patients. Improvements in RA disease activity, HAQ-DI scores, and pain were observed in those who switched.	Study focused on a short-term follow-up period and did not fully address long-term safety outcomes.
Gerlag et al (2020)[56]	Randomized controlled trial (RCT)	N = 81	Rituximab (B-cell depletion therapy)	HAQ-DI	Rituximab treatment showed no significant difference in preventing the development of clinical RA in individuals at clinical high risk.	The study focused only on preclinical RA patients, meaning it may not be applicable to those with more advanced disease.
Glatt et al (2023)[40]	Proof-of-concept, Randomized, Double-blind, Placebo-controlled trial	N = 217 (RA patients with inadequate response to certolizumab pegol)	Bimekizumab (IL-17A and IL-17F inhibitor)	HAQ-DI, VAS	Bimekizumab as add-on therapy showed significant improvements in DAS28 and HAQ-DI compared to placebo.	The study was conducted in a specific patient population (those with an inadequate response to certolizumab pegol), so its applicability to other RA patient populations may be limited.
Globe et al (2008)[45]	Multicenter, Observational, Cross-sectional survey	N = 3010 (patients with RA)	Etanercept	WLPS, HAQ	Etanercept treatment was associated with reduced absenteeism (days missed from work) and improved productivity (work performance) in patients with rheumatoid arthritis.	The study was observational and thus cannot establish a cause-and-effect relationship.
Hetland et al (2020)[57]	Phase IV, Randomised, Observer Blinded Clinical Trial	N = 500 (early RA patients)	Adalimumab, Etanercept, Infliximab, and Conventional DMARDs	HAQ	This study evaluated the efficacy of three biological treatments compared to active conventional treatment in early rheumatoid arthritis (RA).	The study was observer-blinded, but not double-blind, which may introduce some potential bias in outcomes.
Humby et al (2020)[58]	Phase 4, Randomised, Open-label, Multicenter Trial	N = 250 (RA patients, anti-TNF inadequate responders)	Rituximab, Tocilizumab	HAQ	The study compared the efficacy of rituximab and tocilizumab in anti-TNF inadequate responder patients with RA. Both treatments significantly reduced disease activity and improved HAQ.	The study was open-label, which may introduce bias in assessing subjective outcomes like QoL.
Ibrahim et al (2020)[59]	Proof of Principle, Exploratory Trial	N = 50 (RA patients with good response to TNFi)	TNF Inhibitors (TNFi)	HAQ	The study evaluated the feasibility of dose tapering in RA patients who had a good response to TNFi. The trial found that dose tapering was practical in most good responders, with sustained low disease activity in a significant proportion of patients.	Small sample size (50 patients) limits generalizability.

Ines et al (2020)[26]	Observational, Prospective Study	N = 150 (RA patients)	Biologic agents (TNFi, rituximab, tocilizumab)	FSS, HAQ	The study found that biologic therapy significantly improved fatigue in RA patients, with TNF inhibitors, rituximab, and tocilizumab showing positive effects.	The study was observational, with potential bias in patient selection and no control group. The short-term follow-up period might limit understanding of long-term effects.
Kremer et al (2005)[60]	Randomized Controlled Trial (RCT)	N = 634 (RA patients)	CTLA4Ig (Abatacept)	HAQ	The study found that CTLA4Ig (Abatacept) significantly improved clinical outcomes in RA patients, including reduction in improvement in HAQ.	The study primarily focused on short-term efficacy and safety.
Leng et al (2022)[61]	Phase Ia Randomized Placebo-Controlled Study	N = 60 (RA patients)	WBP216 (IL-6 monoclonal antibody)	HAQ	With significant improvements in HAQ observed in the active treatment group compared to placebo.	The study was limited to a short-term phase Ia trial.
Lipsky et al (2000)[38]	Randomized, Double-Blind, Controlled Trial	N = 428	Infliximab + Methotrexate	HAQ, VAS	Infliximab combined with Methotrexate showed significant improvement in disease activity and physical function compared to placebo + Methotrexate. Infliximab also improved radiographic outcomes by inhibiting joint damage progression.	The trial's sample size was large, but the study was relatively short-term.
Martin et al (2013)[62]	Phase Ib, Multiple Ascending Dose Study	N = 107	Brodalumab (Anti-IL -17R Antibody)	HAQ-DI	Brodalumab was well-tolerated and showed a dose-dependent improvement in HAQ-DI. Early clinical responses were observed, particularly with higher doses.	The study was focused on safety and early clinical response, but the follow-up period was short, and long-term efficacy and safety were not evaluated.
Smolen et al (2018)[63]	Randomized, Phase II, Multicenter Study	Varied (typically 100–200 participants per group)	Ustekinumab, Guselkumab (both IL-12/23 inhibitors)	HAQ, PGA	Both Ustekinumab and Guselkumab were found to be effective in reducing disease activity in RA patients with an inadequate response to methotrexate. Significant improvements in HAQ scores were observed.	Small sample size in the Phase II design limits the generalizability of the results to larger populations.
Tan et al (2017)[69]	Observational Research	N = 193	Biological DMARDs (specific biologics not mentioned)	HAQ	Significant improvement in disease activity and functional ability after treatment with biological DMARDs	No direct comparison to non-biological treatments.
Smolen & Kremer et al (2020)[25]	Randomized, Phase III, Multicenter Study	N=1300+	Baricitinib (JAK inhibitor)	HAQ, PGA, EQ-5D, VAS	Baricitinib showed significant improvement in PROs, including HAQ and PGA scores, compared to placebo. Patients reported better QoL and less pain after treatment. Baricitinib provided a significant reduction in fatigue and improved physical function in patients with RA who had an inadequate response to prior biological agents.	The study focused primarily on short-term effects, and long-term safety and efficacy data were not fully explored.
Smolen et al (2020)[64]	Randomized, Placebo-controlled, Double-Blind Phase 3 Study	N=648	Upadacitinib (JAK inhibitor)	HAQ, PGA, EQ-5D, VAS	Upadacitinib showed significant improvement in clinical outcomes including HAQ, PGA, and VAS compared to placebo. Patients also reported better QoL and pain reduction. Upadacitinib as monotherapy was well-tolerated and provided superior efficacy in patients with active RA and an inadequate response to methotrexate.	Limited subgroup analysis; the study primarily focuses on the short-term effects of upadacitinib, with long-term efficacy and safety still needing further investigation.

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Table 1 (Continued).

Study (Year)	Study Design	Sample Size	Biologic Therapy	QoL Measures Used	Main Findings	Key Limitations
Strand et al (2017)[65]	Post hoc analysis of Phase 3 trials	N=3419	Tofacitinib (JAK inhibitor)	PGA, HAQ, VAS, FACIT-Fatigue scale	PGA scores were significantly associated with pain, physical function, and fatigue in rheumatoid arthritis patients treated with tofacitinib. The strongest associations were found between PGA and pain, followed by physical function and fatigue.	Post hoc analysis limits the ability to make definitive causal conclusions.
Strand et al (2020)[66]	Phase IIIB/IV randomized clinical trial	N=1202	Tofacitinib (JAK inhibitor) with or without methotrexate vs Adalimumab + methotrexate	PROs: HAQ, VAS, FSS, PGA, EQ-5D	Patients receiving Tofacitinib with or without methotrexate showed significant improvements in PGA, pain, and fatigue compared to adalimumab + methotrexate.	Open-label design introduces potential bias.
Strand et al (2011)[67]	Randomized, multicenter clinical trial	N=1000	Adalimumab (TNF inhibitor)	HAQ, EQ-5D, Short SF-36, VAS	Patients treated with Adalimumab showed significant improvements in HRQoL, particularly in physical functioning, pain, and general health compared to those receiving placebo. Significant improvements in SF-36 domains and EQ-5D scores.	Open-label design and lack of long-term follow-up limit understanding of long-term benefits.
Feist et al (2024)[68]	Phase III, Double-blind, Randomized Clinical Trial	N=1200 patients with moderate to severe RA	Olokizumab + Methotrexate	SF-36, VAS, HAQ-DI	Sustained improvement in physical function (HAQ-DI scores) and quality of life (SF-36).	Limited to moderate/severe RA
Inotai et al (2011)[30]	Cross-sectional, Non-interventional Study	N=253 total (85 biological, 168 non-biological)	Biological treatments (specific therapies not mentioned)	EQ-5D, VAS, RAQoL	Biological treatment was associated with higher utility of EQ-5D index.	The study is cross-sectional and non-interventional, meaning it does not establish causality between treatment and improvements in QoL.

Abbreviations: AD, Atopic Dermatitis; AS, Ankylosing Spondylitis; bDMARD, Biologic Disease-Modifying Antirheumatic Drug; DAS28, Disease Activity Score 28; DMARD, Disease-Modifying Antirheumatic Drug; EQ-5D, EuroQol 5 Dimension; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FSS, Fatigue severity scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, Methotrexate; NRS, Numeric Rating Scale; PtGA, Patient Global Assessment; PROMIS, Patient-Reported Outcomes Measurement Information System; PsA, Psoriatic Arthritis; RA, Rheumatoid Arthritis; RAQoL, Rheumatoid Arthritis Quality of Life; SF-36, Short Form 36 health Survey; WPAI-RA, Work Productivity and Activity Impairment-Rheumatoid Arthritis; WLPS, Work Loss and Productivity Survey.

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Patient Expectations and Perceptions

Patient expectations and perceptions of biologic therapies significantly influence their reported QoL outcomes. Unrealistically high expectations may lead to dissatisfaction, even when clinical targets are met. Conversely, patients with realistic expectations are more likely to report improved QoL when experiencing symptom relief and functional gains.[77] Studies suggest that shared decision-making, which incorporates patient preferences and educates them on realistic outcomes, enhances treatment satisfaction and perceived QoL improvements.[78] Patient-centered communication that aligns therapeutic goals with individual expectations is thus integral to optimizing QoL outcomes.[79] QoL outcomes in RA are multifactorial, influenced by disease activity, patient characteristics, treatment side effects, and patient expectations. Achieving low disease activity or remission remains the cornerstone of improving QoL, underscoring the importance of individualized treatment strategies.

Challenges and Limitations in Measuring Quality of Life in Rheumatoid Arthritis

Measuring QoL in patients with RA is a critical aspect of understanding the disease's impact and evaluating treatment effectiveness. However, capturing the complexity of QoL is challenging due to the multidimensionality of the concept, the subjective nature of assessments, and methodological inconsistencies. QoL encompasses several domains, including physical, emotional, social, and psychological well-being, all influenced by disease activity, functional limitations, and treatment responses. Instruments like the HAQ and the SF-36 often focus on physical health, underrepresenting psychological and social aspects.[24,80,81] This imbalance can lead to an incomplete assessment of QoL.

Inadequacy of Standardized Tools

Assessing health-related QoL in RA patients presents unique challenges due to the disease's multifaceted nature. While widely used generic tools like the SF-36 and EQ-5D are valuable for evaluating overall health status, they may not fully capture RA-specific symptoms such as joint stiffness, fatigue, and morning stiffness. Studies have shown that patients with RA score significantly lower on physical functioning and bodily pain dimensions of the SF-36 compared to individuals without musculoskeletal diseases, highlighting the substantial impact of RA on physical aspects of health-related QoL.[72] To address these limitations, disease-specific instruments like the Rheumatoid Arthritis Quality of Life (RAQoL) questionnaire have been developed.[30,82] The RAQoL was created directly from patient interviews to ensure relevance to the RA experience and has demonstrated high internal consistency and test-retest reliability. Additionally, the RAQoL has been adapted and validated in multiple languages, facilitating its use in diverse populations.

Despite its robust psychometric properties, the RAQoL's adoption in clinical practice remains limited, possibly due to a lack of awareness or training among healthcare providers. Integrating RA-specific QoL assessments like the RAQoL into routine care could enhance the understanding of patient experiences and improve treatment outcomes.

Dynamic and Fluctuating Nature of Rheumatoid Arthritis

RA is characterized by periods of flares and remission, leading to fluctuations in QoL over time.[1] Cross-sectional assessments often fail to capture these dynamic changes, providing only a static view of the patient's experience.[41] RA flares involve a sudden worsening of symptoms such as joint pain, swelling, and stiffness, which can persist for days to weeks. These episodes disrupt daily functioning and reduce QoL, even when overall disease activity appears controlled. In contrast, periods of remission or low disease activity allow for better functioning and improved well-being.[25] The cumulative effect of repeated flares contributes to joint damage, physical disability, and comorbid conditions such as cardiovascular disease.[5] This progressive nature of RA, influenced by the frequency and severity of flares, underscores the need for effective management strategies. The cumulative effect of repeated flares contributes to joint damage, physical disability, and comorbid conditions such as cardiovascular disease. This progressive nature of RA, influenced by the frequency and severity of flares, underscores the need for effective management strategies.[3] Longitudinal studies and repeated QoL assessments are more effective in reflecting the dynamic course of RA. Tools that track changes over time, such as the DAS28 combined with patient-reported outcomes, offer better insights into the interplay between disease activity and QoL.[83] Including flare frequency, duration, and severity as part of routine QoL assessments provides a more

comprehensive understanding of the disease's impact. Such data are essential for tailoring treatment plans to minimize flares and improve patient outcomes.[81]

Clinical Implication

Impact of Comorbidities

Comorbidities are additional medical conditions that coexist with RA and significantly influence disease outcomes, treatment approaches, and patients' QoL. Patients with RA are at increased risk of developing cardiovascular diseases, including atherosclerosis, myocardial infarction, and stroke. Chronic inflammation is a major contributing factor, as it accelerates vascular damage and lipid metabolism abnormalities.[84–86] This increased cardiovascular risk often necessitates aggressive inflammation control and lifestyle modifications. Chronic inflammation, long-term glucocorticoid use, and reduced physical activity contribute to an elevated risk of osteoporosis and fractures in RA patients.[87] Osteoporotic fractures can severely impair mobility and QoL, necessitating early screening and preventive strategies.[88] Depression and anxiety are prevalent in RA patients, often linked to chronic pain, functional limitations, and social isolation. These mental health conditions further reduce QoL and can hinder adherence to treatment regimens.[72] RA treatments, especially biologics and glucocorticoids, increase susceptibility to infections. This vulnerability complicates disease management, as infections can trigger RA flares and necessitate treatment interruptions.[89] RA patients are more likely to develop metabolic syndrome, characterized by obesity, insulin resistance, and hypertension.[90] This is partly due to systemic inflammation and corticosteroid use, which exacerbate metabolic dysregulation. The presence of comorbidities often limits therapeutic options. Cardiovascular risk factors may preclude the use of certain nonsteroidal anti-inflammatory drugs (NSAIDs), and infections may restrict the use of biologics. The systematic review and meta-analysis titled "Effect of TNF inhibitors on arterial stiffness and intima media thickness in rheumatoid arthritis" by Abdulmajid et al reported that TNF inhibitor therapy in RA patients may favorably influence certain surrogate markers of cardiovascular risk.[91]

RA is not limited to joint pathology; it also involves systemic inflammation that affects organs such as the lungs, heart, and skin.[84–93] Common comorbidities include cardiovascular disease, interstitial lung disease, and osteoporosis. These conditions complicate disease management and contribute to increased morbidity and mortality.[88,94]

RA imposes substantial direct and indirect costs on patients and healthcare systems. Direct costs include medication, hospitalizations, and laboratory monitoring, while indirect costs arise from work absenteeism and loss of productivity. These economic implications underscore the need for cost-effective treatment approaches.[95] Early diagnosis and treatment initiation are critical for preventing joint damage and systemic complications. However, the nonspecific early symptoms of RA often lead to delays in diagnosis, resulting in poorer outcomes.[49] The presence of comorbid conditions complicates the choice of therapies. For example, cardiovascular risk may limit the use of NSAIDs, and infections may preclude biologic treatments.[86,96] Adherence to long-term RA treatment is challenging due to medication side effects, the complexity of treatment regimens, and patient perceptions of efficacy.[23] Nonadherence can lead to disease flares and worse outcomes. Treat-to-target strategies using DMARDs or biologics aim to achieve remission or low disease activity, thereby preventing joint damage and systemic complications.[48] Collaboration between rheumatologists, primary care physicians, psychologists, and other specialists ensures comprehensive management of RA and its associated comorbidities. Educating patients about RA, its progression, and the importance of adherence to the treatment plan.

Conclusion

The findings from this review highlight the significant impact of bDMARDs on the QoL of patients with RA. While these therapies have revolutionized RA treatment by effectively reducing inflammation and preventing joint damage, their influence extends beyond physical health, encompassing mental, emotional, and social well-being. One of the most notable benefits of biologic therapies is their ability to improve physical function by alleviating pain, stiffness, and fatigue. Studies have consistently demonstrated improvements in HAQ-DI scores, supporting the role of biologics in maintaining functional independence. Furthermore, evidence suggests that fatigue reduction associated with biologic

therapy occurs independently of inflammation control, potentially indicating additional mechanisms such as modulation of neuroimmune pathways.

The majority of reviewed studies overemphasized biological therapies. While biologics have revolutionized RA treatment, traditional DMARDs like methotrexate still play a crucial role, especially in resource-limited settings. Integrating biosimilars, personalized treatment approaches, and early intervention strategies has demonstrated potential for optimizing both clinical outcomes and economic efficiency. Holistic management, encompassing regular monitoring, patient education, and multidisciplinary care, remains essential for addressing the diverse challenges of RA.

Disclosure

The authors report no conflicts of interest in this work.

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