

---

# New and Emerging Therapies: Review the Latest Advancements in Rheumatology Treatments, Including Biologic Therapies, Targeted Therapies, Regenerative Medicine, and Novel Drug Development, Assessing their Potential Benefits and Limitations

---

Dr. Murooj Luai Majeed Altimimi\*

\*Assistant Professor in Pharmacology in the Pharmacology Department at Kufa Medical College, Al-Najaf, Iraq.

Corresponding Email: [\\*murooj.altameemi@uokufa.edu.iq](mailto:murooj.altameemi@uokufa.edu.iq)

Received: 11 April 2024

Accepted: 27 June 2024

Published: 12 August 2024

**Abstract:** *This study was contributed to assess clinical outcomes related to the role of biologic therapies, targeted therapies, regenerative medicine, and novel drug development in the treatment of rheumatology patients. Patients and methods: A cross-sectional study of 80 rheumatology different hospitals in Iraq analyzed demographic and clinical data from February 2022 to September 2023. The study included 80 cases who underwent modern treatments and methods within the disease management program. The patients were categorized into remission, low, moderate, and high disease severity. Common symptoms included joint pain, swelling, decreased range of motion, fatigue, muscle weakness, fever, numbness, skin rash, weight loss, and difficulty with daily activities. Treatment data included corticoids, cDMARD, bDMARD, and cDMARD combined bDMARD. The study also assessed patients' quality of life, ranging from 0 to 100, based on physical function, psychological function, emotional and social aspects, and daily activity. A multivariate analysis of risk factors affecting patients with rheumatic diseases was performed. Results: Our results shown that males were 16 cases and females were 64 cases, the smoking rate were 30%, obesity was 50%, hypertension was 80%, diabetes was 55%, and cerebrovascular disease was 30%, and the most common symptoms of rheumatic disease which distribute into patients swelling and tenderness in the joints was 80%, joint pain, and stiffness was 85%, and fatigue was 60%, types of treatments used in patients with rheumatology which contain corticoids included 8 cases, cDMARD included 56 cases, bDMARD included 4 cases, and cDMARD combined bDMARD included 12 cases, and we identify activity rheumatic disease which classified into remission got 36 cases, low got 20 cases, moderate got 16 cases, and high got 8 cases. Conclusion: Patients with rheumatic diseases have benefited from biological therapies, targeted therapies, regenerative medicine, and novel drug development.*



***Keywords: Rheumatoid Arthritis, DAS28 Scale, and Treatments (Corticoids, Cdmard, Bdmard, and Cdmard Combined Bdmard.***

## **1. INTRODUCTION**

Rheumatoid arthritis (RA) is a complex autoimmune disease in which chronic inflammation in the joints leads to progressive small joint erosion and functional disability with significant morbidity [1]. It is estimated to affect 0.5-1% of the world's population and is more common in women than in men. [2]

In the United States alone, approximately 1.3 million people have RA, making it a significant health problem. However, advances in medical research have led to the development of many treatment options that can effectively manage symptoms and even slow the progression of the disease [3 – 6]. Currently, the main strategy for treating RA is the use of drugs known as DMARDs, which stand for disease-modifying anti-rheumatic drugs such as methotrexate and other biologic therapies - TNF inhibitors as well as the use of glucocorticoids. These drugs reduce the pain of inflammation, reduce tissue damage, and slow the progression of joint infection [7,8]. The management plan includes monitoring progress with a screening programme and monitoring side effects. However, there is a significant proportion of the population who are not cured or whose symptoms become uncontrollable. [9]

The usual way to treat RA is to take DMARDs [10]. These work by calming down the immune system so that it fights inflammation less and does not damage your joints. If you have RA, it is better to take methotrexate because it is the most commonly prescribed DMARD for this condition. It should be noted that this drug controls swelling in the joints while protecting them from destruction [11 – 13]. It can be taken by mouth or by injection and has been shown to be effective in controlling symptoms and improving patients' long-term outlook. However, many patients do not respond to methotrexate or cannot tolerate it because of its side effects, so other treatments are needed [14,15]. Other DMARDs used instead of methotrexate include sulfasalazine, leflunomide, and hydroxychloroquine. Doctors often combine these drugs to get the most benefit. However, they can sometimes be harmful, and patients need to be monitored regularly to detect any adverse effects. [16]

There are situations where DMARDs are ineffective in treating symptoms and using biological response modifiers may be the best option [17]. These are also called biologics. These biological therapies have changed the way RA is treated by focusing on specific molecules involved in the inflammatory cascade [18]. Drugs such as TNF inhibitors (including the three different types mentioned above) have been found to be beneficial. The action of TNF inhibitors such as infliximab may involve reducing the activity of TNF also known as adalimumab, etanercept among others. [19 - 21]

Tofacitinib and baricitinib work by inhibiting JAKs, which play a role in the inflammatory signalling cascade associated with RA. While biologics are highly effective for many people with RA, they tend to cost more than conventional DMARDs. In addition, increased susceptibility to infection, hepatotoxicity, and skin reactions are potential consequences of their use. [22]

It is, therefore, important to monitor the use of these drugs carefully and to have regular blood tests [23,24]. In recent years, there has been a growing interest in the use of holistic and other

forms of therapy to manage the symptoms of RA [25]. These include exercise programmes, physiotherapy, occupational therapy, and counselling to help people understand and cope with the psychological aspects of having arthritis [26]. In addition, changes in diet and the use of supplements such as fish oil and turmeric have some benefits in reducing inflammation and improving overall health. [27]

## **2. RELATED WORK**

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints and tendon sheaths that can destroy the joints. It is the most common inflammatory rheumatic disease. Although at present, unfortunately, the disease is still incurable, in recent years innovative drug therapies have been developed that allow to significantly improve the quality of life of patients. Research confirms that the earlier you take action on the disease, the more likely you are to continue to lead a normal life. With a few tricks and medications, many people with RA are able to lead an almost normal daily life. Therefore, it is very important to seek medical attention (rheumatologist) if symptoms such as morning stiffness and joint pain persist. The review discusses the latest advancements in rheumatology treatments, including biologics, targeted therapies, regenerative medicine, and novel drug development, evaluating their potential benefits and limitations. In RA, there is an overreaction of the immune system, which does not recognize the synovial membrane and considers it a foreign body, triggering an immune reaction, that is, inflammation. Unlike normal inflammation, this inflammation cannot heal because the "crazy" immune system continues to produce T and B cells that cause joint inflammation. The review discusses the latest advancements in rheumatology treatments, including biologics, targeted therapies, regenerative medicine, and novel drug development, evaluating their potential benefits and limitations. Review the latest advancements in rheumatology treatments Early treatment of rheumatoid disease, especially with methotrexate, in addition to other medications to help control the disease. Multivariate analysis of risk factors affecting patients with rheumatic diseases.

## **3. PATIENTS AND METHODS**

We conducted a cross-sectional study of rheumatology patients, which included 80 cases who underwent all modern treatments and methods within the disease management programme conducted in different hospitals in Iraq. The study period was from 7 February 2022 to 24 September 2023. This study collected demographic and clinical data including age, sex, body mass index classified into (underweight, normal weight, overweight, and obese), smoking status, family history of the disease, previous surgeries, duration of the disease, and comorbidities including (obesity, hypertension, diabetes, chronic renal failure, cerebrovascular disease, heart disease, lung disease, and asthma), and level of education and income of the patients. The study also recorded the most common symptoms in rheumatism patients, including joint pain and stiffness, swelling and pain in the joints, decreased range of motion, fatigue, muscle weakness, fever, numbness or tingling in the hands or feet, skin rash, weight loss, and difficulty with daily activities.

Eighty patients were receiving rheumatology care, with disease management provided by specialist clinics that recorded the number of annual visits to each service area, including rheumatology, physical medicine and rehabilitation, nutrition, psychology, physiotherapy, occupational therapy, and education. Accordingly, this study identified treatment data including corticoids, cDMARD, bDMARD, cDMARD combined bDMARD, and determined the disease management of patients treated for more than seven months according to the Disease Activity Scale DAS28, which was classified into remission (DAS28 <2.6), low (DAS28  $\geq$ 2.6 and <3.2), moderate (DAS28  $\geq$ 3.2 and <5.1), high (DAS28  $\geq$ 5.1). In addition, the prevalence of complications was distributed across all rheumatology patients. Patient's quality of life after rheumatology treatment was also assessed and ranged between (0 - 100), with 0 representing the poor quality of life and 100 representing the optimal quality of life, determined within criteria that included all (physical function, psychological function, emotional, social aspects, and daily activity). We performed a multivariate analysis of risk factors affecting patients with rheumatic diseases.

#### 4. RESULTS AND DISCUSSION

Table 1: Demographic and clinical features of rheumatoid arthritis (RA) patients.

Features	Number of patients (n = 80)	Percentage [%]
<b>Age</b>		
40 – 50	12	15%
51 – 60	20	25%
61 – 70	48	60%
<b>Sex</b>		
Male	16	20%
Female	64	80%
<b>BMI, kg/m<sup>3</sup></b>		
Underweight	12	15%
Normal weight	4	5%
Overweight	24	30%
Obesity	40	50%
<b>Smoking status</b>		
Yes	24	30%
No	56	70%
<b>Family history of the disease</b>		
Yes	20	25%
No	60	75%
<b>Previous surgery</b>		
Yes	28	35%
Mo	52	65%
<b>Disease duration (years)</b>	3.6 $\pm$ 1.02	
<b>Morbidities</b>		
Obesity	40	50%

Hypertension	64	80%
Diabetes	44	55%
Chronic Kidney disease	20	25%
Cerebrovascular disease	24	30%
Heart diseases	16	20%
Pulmonary disease	12	15%
Asthma	8	10%
<b>Education status</b>		
Not in the school	8	10%
Primary	12	15%
Secondary	16	20%
College/university	44	55%
<b>Monthly income, \$</b>		
< 800	40	50%
800 – 1000	24	30%
> 1000	16	20%

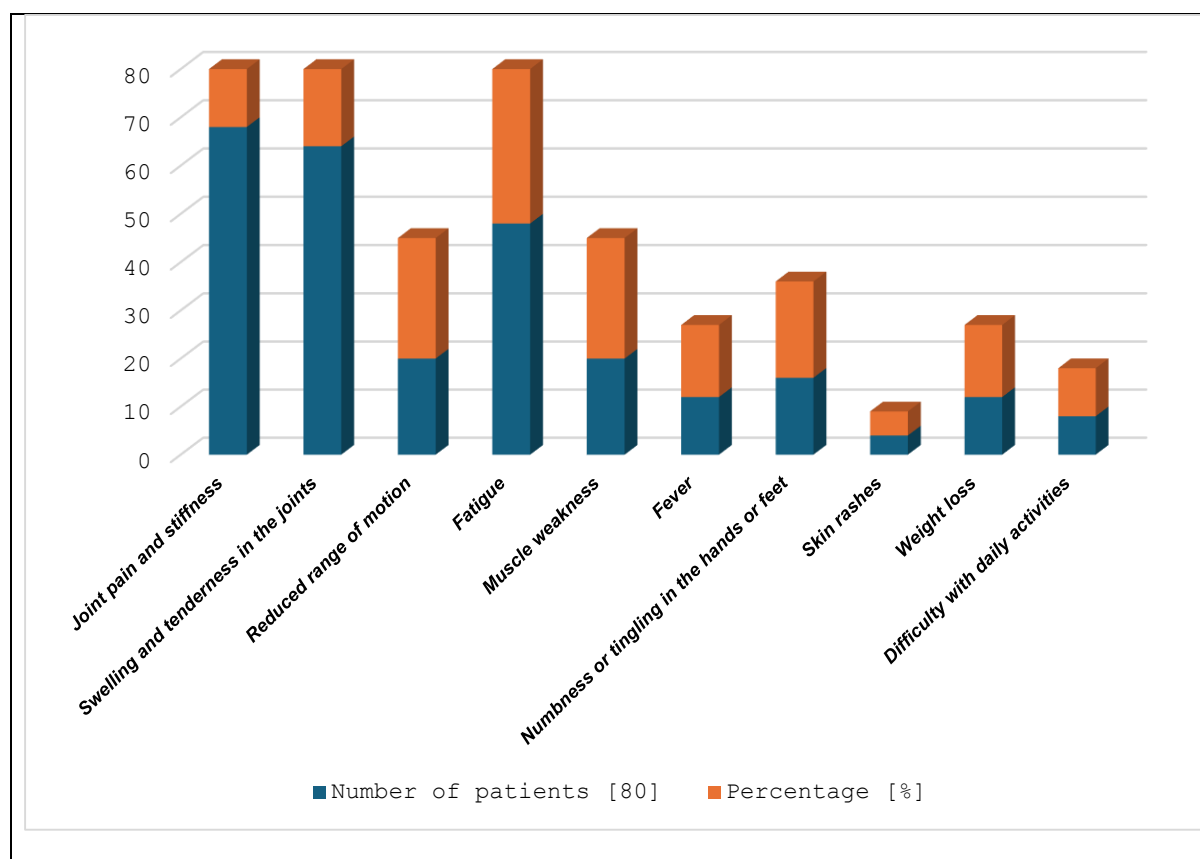


Figure 1: Identification of main symptoms prevalence in patients with rheumatology.

Table 2: Disease management in specialized hospitals in terms of the number of visits per year.

Items	Disease Activity		
	High	Moderate	Low
Rheumatology	10	5	3
Physical Medicine and Rehabilitation	5	4	2
Nutrition	3	2	1
Psychology	5	4	1
Physical therapy	7	3	1
Occupational therapy	6	3	2
Educational sessions	7	4	2
<b>Total</b>	<b>43</b>	<b>25</b>	<b>12</b>

Table 3: Determination of Types of treatments used in patients with rheumatology.

Treatments	Number of patients (n = 80)	Percentage [%]
Corticoids	8	10%
cDMARD	56	70%
bDMARD	4	5%
cDMARD combined bDMARD	12	15%

Table 4: Diseases management of patients who underwent treatment for more than seven months by disease activity DAS28 scale.

DAS28 scale	Number of patients (n = 80)	Percentage [%]
Remission (DAS28 <2.6)	36	45%
Low (DAS28 ≥2.6 and <3.2)	20	25%
Moderate (DAS28 ≥3.2 and <5.1)	16	20%
High (DAS28 ≥5.1)	8	10%

Table 5: Distribution of complications related to patients after treatments received.

Complications	Number of patients (n = 80)	Percentage [%]
Infection	6	7.5%
Gastritis	5	6.25%
Cardiovascular issues	2	2.5%
Osteoporosis	2	2.5%
Liver and kidney damage	1	1.25%
<b>Total</b>	<b>16</b>	<b>20%</b>

Table 6: Assessment of quality of life in patients who underwent to program treatment of rheumatology.

Items	QoL scores
Physical function	72.51 ± 4.81
Psychological function	69.85 ± 5.05
Emotional and social aspects	73.87 ± 3.38



Daily activity	74.40 ± 4.20
----------------	--------------

Table 7: Multivariate analysis of risk factors affecting patients with rheumatic disease.

Risk factors	OR	CI 95%
Age [60 - 70]	3.61	0.60 ± 5.91
Sex [females]	2.65	2.1 ± 4.48
Rheumatoid arthritis	4.70	3.37 ± 6.88
Smoking	8.80	4.35 ± 9.78
Infection	6.50	2.75 ± 9.86
Obesity	5.30	3.21 ± 7.54
Autoimmune diseases		

### Discussion

Our study showed the clinical and demographic results of patients with rheumatic disease, which found patients with age (61 -70) years had the highest rate with 60%, followed by patients with age (51 -60) years had rate with 25%, and patients with age (40 - 50) years were 15%, Males were 16 cases, and females were 64 cases, BMI classifications consisted of underweight with 12 cases, normal weight with 4 cases, overweight with 24 cases and obesity with 40 cases, smokers rate was 30%, and non-smokers was 70%, family history of the disease included 20 cases, disease duration was 3. 6 ± 1.02 years, morbidities included the most common diseases affected on patients, which are obesity was 50%, hypertension was 80%, diabetes was 55%, and cerebrovascular disease was 30%. In Figure 1, our study was determined to be the most common symptoms of rheumatic disease, which were distributed in patients: swelling and tenderness in the joints was 80%, joint pain, and stiffness was 85%, and fatigue was 60%. According to disease management in specialist hospitals, we determined the number of visits to hospitals where the number of visits for patients with high disease activity was 43 visits, the number of visits for patients with moderate disease activity was 25 visits, and the number of visits for patients with low disease activity was 12 visits. In addition, we determined the types of treatments used in patients with rheumatology containing corticoids included 8 cases, cDMARD included 56 cases, bDMARD included 4 cases, and cDMARD combined bDMARD included 12 cases. Based on DAS28 scores, we identify rheumatic disease activity classified into remission got 36 cases, low got 20 cases, moderate got 16 cases, and high got 8 cases. In addition, we identify QoL assessment of general life, which showed physical function was 72.51 ± 4.81, psychological function was 69.85 ± 5.05, emotional and social aspects were 73.87 ± 3.38, and daily activity was 74.40 ± 4.20. We also identified common risk factors affecting patients, which were age [60 - 70], gender [female], rheumatoid arthritis, smoking, infections, obesity, and autoimmune diseases.

Biologic treatments are made from living organisms and target certain elements of the immune system to reduce inflammation and halt disease progression. Their effectiveness has greatly increased survival rates for these patients by helping to relieve symptoms, minimise suffering or halt joint destruction.

On the other hand, targeted therapies have been developed to specifically target abnormal cells or pathways involved in causing rheumatic diseases [29]. Essentially, such treatments have the ability to be individualised and precise because they focus on the main causes of these



disorders, thereby reducing the severity of side effects while increasing their overall effectiveness. [30,31]

The use of tissue engineering, stem cell therapy, and other restorative methods represents a potentially effective way of treating rheumatic diseases by harnessing the body's own repair mechanisms to repair damaged tissues and joints. In this way, these strategies may help to restore function and improve the quality of life of people suffering from debilitating rheumatic diseases. [33]

In addition, recent advances in drug development have led to the discovery of new medicines that target specific pathways and mechanisms in connective tissue diseases (rheumatological diseases). These cutting-edge medicines offer patients more options for managing their disease and achieving positive outcomes. [34,35]

## **5. CONCLUSION**

In conclusion, the significance of other drug therapies, targeted therapies, cell-based treatments, or the development of new drugs in managing patients with rheumatology cannot be overemphasized. This has changed how people with these difficult disorders receive health care through fresh expectations and better standards of living.

## **6. REFERENCES**

1. P. Santos-Moreno, O. Castañeda, B. Garro, D. Flores, G. Sánchez, C. Castro, "From the model of integral attention to the creation of centers of excellence in rheumatoid arthritis," *Clin Rheumatol*, vol. 34, no. S1, pp. 71-77, 2015.
2. P. Santos-Moreno, C. Galarza-Maldonado, C.V. Caballero-Uribe, et al., "REAL-PANLAR project for the implementation and accreditation of centers of excellence in rheumatoid arthritis throughout Latin America: a consensus position paper from REAL-PANLAR group on the improvement of rheumatoid arthritis care in Latin America establishing centers of excellence," *J Clin Rheumatol*, vol. 21, no. 4, pp. 175-180, 2015.
3. P. Santos-Moreno, C.V. Caballero-Uribe, M.H. Cardiel, et al., "A consensus position paper from REAL-PANLAR group about the methodological approach for the accreditation process of centers of excellence in rheumatoid arthritis in Latin America," *J Clin Rheumatol*, vol. 25, no. 1, pp. 54-58, 2019.
4. P.I. Santos-Moreno, J. de la Hoz-Valle, L. Villarreal, A. Palomino, G. Sánchez, C. Castro, "Treatment of rheumatoid arthritis with methotrexate alone and in combination with other conventional DMARDs using the T2T strategy. A cohort study," *Clin Rheumatol*, vol. 34, no. 2, pp. 215-220, 2015.
5. M.A. Stoffer, J.S. Smolen, A. Woolf, et al., "Development of patient-centered standards of care for rheumatoid arthritis in Europe: the eumusc.net project," *Ann Rheum Dis*, vol. 73, no. 5, pp. 902-905, 2014.
6. Ministerio de Salud y Protección S. Política de atención integral en salud. Minsalud; 2016:1-94.
7. Pan American Health Organization. Access to High-Cost Medicines in the Americas: Situation, Challenges and Perspectives. 2010:81.





8. Hu H, Luan L, Yang K, Li S-C. Burden of rheumatoid arthritis from a societal perspective: a prevalence-based study on the cost of illness for patients with rheumatoid arthritis in China. *Int J Rheum Dis*. 2018;21(8):1572–1580.
9. Barrera Castro SM, Suárez Moya ÁMG, Mora LM, Cardona C, Jáuregui Cuartas EA, Muñoz Urrego YA. Aproximación de discapacidad en artritis reumatoide. Resultados de un programa de atención integral. *Rev Colomb Reumatol*. 2017;24(3):138–144.
10. Santos-Moreno P, Caballero-Uribe CV, Massardo ML, et al. Systematic and progressive implementation of the centers of excellence for rheumatoid arthritis: a methodological proposal. *Clin Rheumatol*. 2017;36(12):2855–2858.
11. O. Valencia, G. Lopes, P. Sánchez, L. Acuña, D. Uribe, J. González, "Incidence and prevalence of cancer in Colombia: the methodology used matters," *J Glob Oncol*, vol. 4, pp. 1-7, 2017.
12. Ministerio de Salud y Protección Social, "Resolución 5926 De 2014," 2014, pp. 1-48.
13. T. Bossert, "Comparative Review of Health System Integration in Selected Countries in Latin America," Inter-American Development Bank, (IDB Technical Note; 585), Available: <https://publications.iadb.org/en/publication/11898/comparative-review-health-system-integration-selected-countries-latin-america>, January 2014.
14. MSPS, "Resolucion 1393 De 2015," Colombia, 2015, pp. 14. Available: [https://cuentadealtocosto.org/site/images/Resolucion 1393 de 2015 - ARTRITIS.pdf](https://cuentadealtocosto.org/site/images/Resolucion%201393%20de%202015%20-%20ARTRITIS.pdf). Accessed: October 20, 2020.
15. J. Yazdany, R. Myslinski, T. Johansson, S. Kazi, "Practices participating in the ACR's rheumatology informatics system for effectiveness (RISE) national registry show improvements in quality of care," *Ann Rheum Dis*, vol. 79, pp. 2-80, 2017. Available: <http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2017-eular.5640>. Accessed: October 20, 2020.
16. J.S. Smolen, R. Landewé, F.C. Breedveld, et al., "EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update," *Ann Rheum Dis*, vol. 73, no. 3, pp. 492-509, 2014. doi: 10.1136/annrheumdis-2013-204573.
17. M.L.L. Prevoo, M.A. Van't Hof, H.H. Kuper, M.A. Van Leeuwen, L.B.A. Van De Putte, P.L.C.M. Van Riel, "Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis," *Arthritis Rheum*, vol. 38, no. 1, pp. 44-48, 1995. doi: 10.1002/art.1780380107.
18. Bruce B, Fries JF. "The stanford health assessment questionnaire: dimensions and practical applications." *Health Qual Life Outcomes*. 2003;1:20. DOI: 10.1186/1477-7525-1-20
19. Pilar C, Camargo B, Eliana L, Ruiz G. "Análisis de la Variación de los Costos de los Medicamentos de Artritis Reumatoide en Una eps en la Ciudad de Bogotá, 2009 – 2011." Pontificia Universidad Javeriana; 2012. Available from: <https://repository.javeriana.edu.co/bitstream/handle/10554/1847/BecerraCamargoClaudiaPilar2012.pdf?sequence=1>. Accessed October 20, 2020.



20. Lurie JD, Bell JE, Weinstein J. "What rate of utilization is appropriate in musculoskeletal care?" *Clin Orthop Relat Res.* 2009;467(10):2506–11. DOI: 10.1007/s11999-009-0889-4
21. Badamgarav E, Croft JD, Hohlbauch A. "Effects of disease management programs on the functional status of patients with rheumatoid arthritis." *Arthritis Rheum.* 2003;49(3):377–387. DOI: 10.1002/art.11120
22. Gleason PP, Alexander GC, Starner CI, et al. "Health plan utilization and costs of specialty drugs within four chronic conditions." *J Manag Care Pharm.* 2013;19(7):542–548.
23. A. A. Kawatkar, S. J. Jacobsen, G. D. Levy, S. S. Medhekar, K. V. Venkatasubramaniam, and L. J. Herrinton, "Direct medical expenditure associated with rheumatoid arthritis in a nationally representative sample from the medical expenditure panel survey," *Arthritis Care Res.*, vol. 64, no. 11, pp. 1649–1656, 2012.
24. P. M. Brooks, "The burden of musculoskeletal disease—a global perspective," *Clin Rheumatol.*, vol. 25, no. 6, pp. 778–781, 2006.
25. C. J. Michet, K. Strobova, S. Achenbach, C. S. Crowson, and E. L. Matteson, "Hospitalization rates and utilization among patients with rheumatoid arthritis: a population-based study from 1987 to 2012 in Olmsted County, Minnesota," *Mayo Clin Proc.*, vol. 90, no. 2, pp. 176–183, 2015.
26. A. M. Briggs, R. E. Fary, H. Slater, et al., "Disease-specific knowledge and clinical skills are required by community-based physiotherapists to co-manage patients with rheumatoid arthritis," *Arthritis Care Res.*, vol. 64, no. 10, pp. 1514–1526, 2012.
27. M. J. H. Voshaar, I. Nota, M. A. F. J. Van De Laar, and B. J. F. Van Den Bemt, "Patient-centered care in established rheumatoid arthritis," *Best Pract Res Clin Rheumatol.*, vol. 29, no. 4–5, pp. 643–663, 2015.
28. P. A. Laires, F. Exposto, R. Mesquita, A. P. Martins, L. Cunha-Miranda, and J. E. Fonseca, "Patients' access to biologics in rheumatoid arthritis: a comparison between Portugal and other European countries," *Eur J Heal Econ.*, vol. 14, no. 6, pp. 875–885, 2013.
29. R. Ruiz, K. Strasser-Weippl, D. Touya, et al., "Improving access to high-cost cancer drugs in Latin America: much to be done," *Cancer*, vol. 123, no. 8, pp. 1313–1323, 2017.
30. K. Michaud, N. Berglind, S. Franzén, et al., "Can rheumatoid arthritis (RA) registries provide contextual safety data for modern RA clinical trials? The case for mortality and cardiovascular disease," *Ann Rheum Dis*, vol. 75, no. 10, pp. 1797–1805, 2016.
31. V. Navarro-Compán, J.S. Smolen, T.W.J. Huizinga, et al., "Quality indicators in rheumatoid arthritis: results from the METEOR database," *Rheumatol*, vol. 54, no. 9, pp. 1630–1639, 2015.
32. S. Mahmood, N. Lesuis, L.H.D. Van Tuyl, P. Van Riel, R. Landewé, "Quality in rheumatoid arthritis care," *Best Pract Res Clin Rheumatol*, vol. 29, no. 4–5, pp. 664–679, 2015.
33. Y. El Miedany, "Adopting patient-centered care in standard practice: pROMs are moving toward a disease-specific era," *Clin Exp Rheumatol*, vol. 32, pp. S40–S46, 2014.



34. B.C.M. Wang, P-N. Hsu, W. Furnback, et al., "Estimating the economic burden of rheumatoid arthritis in Taiwan using the National Health Insurance Database," *Drugs Real World Outcomes*, vol. 3, no. 1, pp. 107–114, 2016.
35. Ministerio de Salud, "Resolución 8430 De 1993," vol. 1993 Minist Salud y Protección Soc República Colomb, pp. 1–19, Octubre 4, 1993.