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ORIGINAL RESEARCH

Adherence to Subcutaneous Anti-Tumour Necrosis Factor Treatment in a Cohort of Patients with Rheumatoid Arthritis Before and After the Implementation of a Comprehensive Care Model

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Purpose: To assess, in a cohort of patients with rheumatoid arthritis (RA) treated with subcutaneous antitumor necrosis factor drugs (anti-TNFs), the levels of treatment adherence before and after implementing a comprehensive care model (CCM).

Patients and Methods: An observational study including RA patients under treatment with subcutaneous anti-TNFs (adalimumab, etanercept, and golimumab) selected at convenience was performed; a sample size of 125 patients was calculated. The outcome variable was adherence assessed with the Compliance Questionnaire on Rheumatology (CQR19), measured before and after implementing a CCM. Descriptive and bivariate analyses were performed comparing adherence before and after applying the model (Wilcoxon and McNemar's Chi^2 test). For multivariate analysis, a generalized linear model adjusted for covariates was performed, where the difference in the proportion of adherence was the outcome measure.

Results: A total of 131 RA patients were followed-up for 24 months; average age was 62 years, and 83.9% were women. The median of DAS28 at the beginning of the follow-up was 2.32, and the HAQ was 0.25. At baseline, 87.8% were adherent; after 24 months, 96.2% were adherent according to CQR19. At the end of follow-up, adherence increased with the three types of anti-TNFs treatment. In a matched model adjusted for clinical variables, the CCM was estimated to produce a 9.4% increase in the total percentage of adherent patients. Additionally, a statistically significant increase of 4.5% in the percentage of adherent patients treated with golimumab compared with etanercept and adalimumab was found.

Conclusion: A CCM produced an important increase in the percentage of patients with rheumatoid arthritis adherent to treatment after 24 months of follow-up. It is noteworthy that Golimumab patients were more adherent when compared with other current anti-TNFs treatments.

Keywords: rheumatoid arthritis, treatment adherence, comprehensive health care, antirheumatic agents, controlled before–after studies

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases, characterized by the presence of autoantibodies, inflammatory and symmetric joint involvement triggering pain and polyarticular edema.[1,2] Its evolution tends to be progressive due to synovial damage, destruction of cartilage and bone erosions. Additionally, it generates

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significant disability,[3,4] extra-articular symptoms, involvement of other systems and increased mortality.[1] The constant inflammatory response is perpetuated by the production and activation of interleukin 2, interferon ɣ, autoantibodies, B cells, and tumor necrosis factor α (TNFα) among other cytokines.[2] This argues the importance of early diagnosis and treatment. A therapeutic option is related to disease-modifying antirheumatic drugs (DMARDs), which in addition to acting on the inflammatory condition, prevents joint damage by restriction of the progression of the disease and improving physical function. Tumor necrosis factor inhibitors (anti-TNFs) are a subtype of biological DMARDs that neutralize TNFα and therefore the subsequent inflammatory process, cartilage damage and bone degradation.[2,5] An important aspect of the disease treatment is the follow-up, under the treat to target (T2T) strategy,[6] by the physician, at least every 3 months or depending on diseases activity; at the same time, it is important to verify patient's adherence to DMARDs, which in the present study are biological DMARDs.

The clinical evolution of autoimmune joint diseases, prognosis and health outcomes are related to timely initiation of the indicated treatment, as well as adherence to it by the patient.[1] Poor adherence leads to therapeutic failure, clinical relapses, increased morbidity and unnecessary changes of dosage or treatment.[5,7] On the other hand, proper adherence with indicated treatment increases its effectiveness, reduces the disease burden, improves quality of life, and reduces the costs and implications derived from the illness. Although the beneficial effects of being adherent to treatment are well known, different social, economic, psychological, and clinical situations have been described that could hamper the treatment continuity according to its prescription. For the treatment of RA, adherence figures vary and depend on multiple factors, ranging from 20% to 80%.[5,7–10]

Variability in RA treatment adherence could be the result of different factors such as absence of following standard guidelines, the limited interaction between patients and health providers, the fragmentation in terms of quality of health care, the poor knowledge regarding the reasons for low adherence, and the social inequities among others; despite the fact that these aspects do not depend exclusively on the patient, they are related to and influence the continuity of the prescribed management. Therefore, different elements must be considered when intended to modify therapeutic adherence in chronic diseases such as RA.[11]

In the persistent search for actions to mitigate non-adherence with medication prescriptions, effective continuity methods, technological tools, educational activities, and different care models have been proposed to improve adherence to pharmacological management.[12] Accordingly, the objective of the present study was to assess, in a cohort of RA patients under subcutaneous anti-TNFs therapy, the levels of treatment adherence, before and after the implementation of a comprehensive care model (CCM) in a rheumatology reference center in Bogotá, Colombia.

Materials and Methods

Design

An observational study was carried out from a cohort of patients with RA treated with subcutaneous anti-TNF drugs, in whom measurements of adherence to treatment were made, before and during the 24 months after the implantation of CCM.

Sampling and Sample Size

A non-probabilistic sampling, sequential for convenience, and for the calculation of the sample size, was made. According to the results reported by Stockl et al,[13] a difference in the proportion of adherence was estimated, before and after the intervention of 23%, going from 60% pre-intervention to 83% post-intervention. A significance level of 95%, power of 80% and a ratio of exposed to unexposed of 1, was established, for a calculated sample size of 125 patients.

Participants

All the patients of ≥18 years old, diagnosed with RA according to the criteria of the ACR/EULAR 2010,[14] under subcutaneous anti-TNF treatment during the last 12 months, able to provide information of adherence at the beginning, and during the follow-up, and who signed the consent form were consecutively included. Pregnant women or women with short-term reproductive desire were excluded. Patients who shifted to another anti-TNF drugs other than the baseline anti-TNF were not included.

Exposition

A CCM was implemented as part of routine management, which is offered to all patients treated at the healthcare rheumatology center (Figure 1). The CCM includes individualized care based on evidence-based guidelines and institutional protocols, treatment guided by clinical goals, therapy administration, construction of effective communication channels, validated measurement of disease activity, and non-fragmented comprehensive care by an multidisciplinary team which includes rheumatologists, physical and rehabilitation medicine, psychologists, physiotherapists, nutritionists, occupational therapists, nurses, and pharmaceutical chemists by periodical appointments; regarding rheumatology assessment, consultations are provided monthly in case of high or moderate disease activity, and every 3 months in case of low disease activity or remission.

Procedure

The levels of adherence were measured at baseline and after the implementation of the CCM, prospectively every 6 months, for a period of 24 months.

The outcome variable of this research was adherence, measured through the 19-item Compliance-Questionnaire-Rheumatology (CQR19) scale, (Supplementary material 1), composed of 19 items, with a total score ranging from 0 (no adherence) to 100 (perfect adherence). In addition, it can be analyzed using the estimated cut-off point for the Colombian population of 80.7 points.[15] Outcomes were measured every 6 months for a period of 24 months. In addition, electronic medical records were reviewed, and patient interviews were done to obtain information about demographic and baseline characteristics such as gender, age, and clinical disease characteristics. Disease activity was measured using the Disease Activity Score with 28-joint counts (DAS28) [interpreted as high (DAS28 >5.1), moderate (DAS28 ≤5.1–≥3.2), low

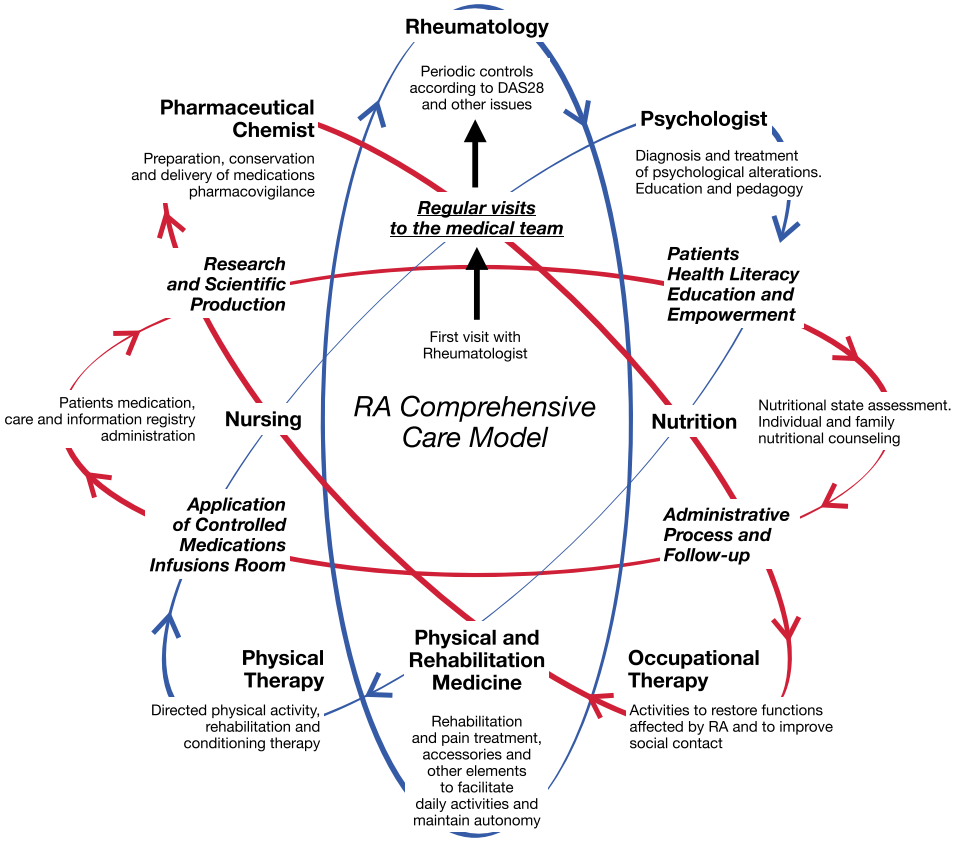

Figure 1 Comprehensive care model implemented at the healthcare rheumatology center. The first visit within the model is made by the rheumatologist, later the patient goes through the other health specialties depending on the determined needs identified and the disease activity level.
Abbreviations: DAS28, Disease Activity Score for 28 joints; RA, rheumatoid arthritis.

(DAS28 <3.2–≥2.6), and remission (DAS-28216 <2.6)]. Disability was assessed using the Health Assessment Questionnaire (HAQ).[16,17]

Analysis

For this analysis, the quantitative variables were expressed using measures of central tendency and dispersion, while the qualitative ones through frequency tables with absolute and relative values. A bivariate analysis was made comparing the distribution of treatment adherence scores according to CQR19, before and after exposure to the CCM. Each patient had a baseline adherence measurement and four measurements after CCM implementation. The comparison of the adherence level distribution was made between the baseline evaluation and the evaluation at the end of follow-up (month 24). Since the data did not present a normal distribution, this comparison was made using the Wilcoxon nonparametric test for paired data.

Additionally, the association between adherence (cut-off point of CQR19: 80.7) and the implementation of the CCM was evaluated. For this contrast, the baseline measurement and the one at 24 months were compared applying McNemar's Chi^2 statistical test. Analyses were performed using STATA IC16 software.

Ethics Approval

During the study, the local ethical principles of the Ministry of Health of Colombia, and the Declaration of Helsinki and the Belmont Report were considered. This project was endorsed and monitored by an independent ethics committee – CEISH (Comite de Etica Independiente Hospital San Jose, act number 008–27th September 2017). Each subject who agreed to be part of this research previously had anti-TNF treatment and received a detailed explanation about the objectives and scope of the study, and voluntarily signed the informed consent. The healthcare provided by this institution to patients who did not authorize follow-up was not affected.

Results

A total of 173 patients were included at CCM, 131 completed 24 months of follow-up, 42 were not included into the analysis (Figure 2). In total, 110 were women, the average age was 62 years with a range between 30 and 84 years. In this cohort, patients were treated with one of three subcutaneous anti-TNF drugs, adalimumab, etanercept, and golimumab. At the end of follow-up, the distribution between the different anti-TNF drugs varied as follows: etanercept 51 cases (38.9%); golimumab 37 cases (28.2%); and adalimumab 43 cases (32.8%). The median disease activity measured with DAS28 at the start of follow-up was 2.32 [interquartile range (IQR): 2.1–2.95], while the median HAQ was 0.25 (IQR: 0–0.75). Table 1 presents the details of the sociodemographic characteristics.

Adherence Evaluation – CQR19

The median baseline CQR19 was 87.7 points, and after 24 months of the CCM implementation it increased to 91.2 points (p value: <0.001). Considering the cut-off point of 80.7 to establish adherence according to the CQR19, at the time of the baseline measurement 87.8% of patients (n=115) were considered adherent, while at the end of follow-up it reached 96.2% (n=126), for a difference in proportions of 8.39% (95% CI 1.9–14.9%; p value=0.012). Table 2 shows the behavior of the CQR19 throughout the follow-up.

Adherence and Type of Anti-TNF

The percentage of adherent RA patients by type of anti-TNF treatment at the time of baseline measurement was in a range of 86.8% to 88.8%. After 24 months of follow-up, adherence increased in all types of treatment with values between 93.9% and 100%. The highest difference in proportions was for Golimumab, which differed from 86.8% adherence at baseline to 100% adherence at the end of follow-up (difference in proportions: 13.1%; CI95: 2.4–23.9; p-value: 0.02). Table 3 shows the adherence behavior by anti-TNF treatment type.

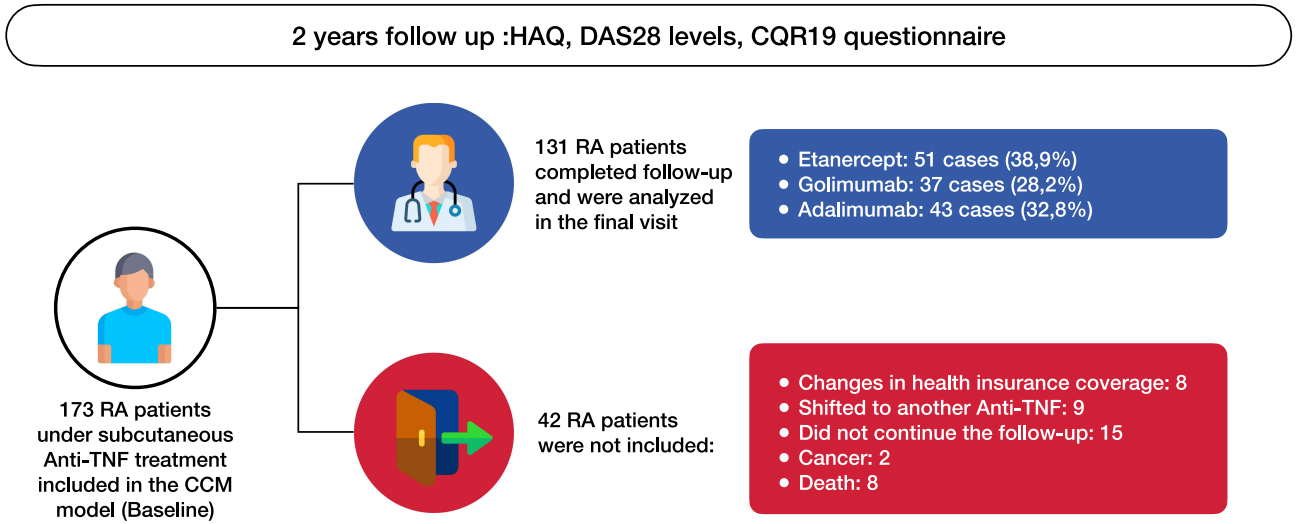

Figure 2 Patients included during the follow-up.
Abbreviations: Anti-TNF, antitumor necrosis factor drugs; CCM, comprehensive care model; DAS28, Disease Activity Score for 28 joints; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis.

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Table 1 Sociodemographic Characteristics of Patients Under Anti-TNFs Subcutaneous Treatment with Rheumatoid Arthritis

Variables		n (%)
Gender n=131	**Women**	110 (83.9)
	Men	21 (16.1)
Age - Mean (SD)		62 (9.9)
Subcutaneous anti-TNF treatment used	**Etanercept**	49 (37.4)
	Golimumab	38 (29.0)
	Adalimumab	44 (33.6)
DAS28 – Median (IQR)	**At the start of follow-up**	2.32 (2.1–2.95)
	At the end of follow-up	2.38 (2–3.17)
HAQ – Median (IQR)	**At the start of follow-up**	0.25 (0–0.75).
	At the end of follow-up	0.13 (0–0.38)

Abbreviations: DAS28, Disease Activity Score for 28 joints; HAQ, Health Questionnaire Assessment; IQR, interquartile range; anti-TNF, antitumor necrosis factor drugs.

Table 2 Behavior of Adherence During Follow-Up Using CQR19

Variable	Baseline	6 Months	12 Months	18 Months	24 Months
CQR19 Median (IQR)	87.7 (84.2–91.2)	89.4 (85.9–92.9)	91.2 (87.7–94.7)	92.9 (87.7–94.7)	91.2 (87.7–94.7)
CQR19 ≥80.7 (adherence) n (%)	115 (87.8)	117 (89.3)	124 (94.7)	130 (99.2)	126 (96.2)

Abbreviations: CQR19, 19-item Compliance-Questionnaire-Rheumatology; IQR, interquartile range; CQR19 ≥80.7, estimated cut-off point of good adherence for the Colombian population.

Table 3 Adherence According to Anti-TNF Treatment Type Received

Anti-TNF	Baseline Adherence		Final Adherence		Difference (%)	95% CI		P value
	n	%	n	%				
Etanercept (n=49)	43	87.7	46	93.9	6.1	(-)5.2	17.5	0.29
Golimumab (n=38)	33	86.8	38	100	13.1	2.4	23.9	0.02
Adalimumab (n=44)	39	88.6	42	95.4	6.8	(-)4.3	18	0.23
Total	115	87.8	126	96.2	8.4	1.9	14.9	0.01

Abbreviations: CI, confidence interval; Anti-TNF, antitumor necrosis factor drugs.

Multivariate Analysis

The multivariate analysis model matched for the variables of age and sex, and adjusted for the covariates DAS28, HAQ, and type of anti-TNF drug, allowed us to estimate that CCM produces an increase in the percentage of adherent patients of 9.4% (CI95%: 3.2–15.5; p-value: 0.003). Additionally, it was possible to establish that, adjusted by the effect of CCM, and the other covariates described, Golimumab produces an increase of 4.5% in the percentage of patients who are adherent to treatment after 24 months, compared to etanercept and adalimumab (CI95%: 0.5–8.5; p-value: 0.024). The details of the multivariate analysis are presented in Table 4.

Table 4 Factors Associated with Adherence to Treatment According to the Cut-Off Point ≥80.7 of the CQR19. Model Matched by Age and Gender

Independent Variables		DP[§] (%) 95% CI	P value
Intervention	Before the CCM	1	
	After the CCM	9.4 (3.2–15.5)	0.003
Anti-TNF Type	Etanercept–Adalimumab	1	
	Golimumab	4.5 (0.5–8.5)	0.024
DAS-28		−0.85 (−3.2–14.9)	0.47
HAQ		0,00 (−0.03 −0.045)	0.85

Notes: [§]Difference in adherence proportions (24 months-baseline), estimated with the identity link function.
Abbreviations: CI, confidence interval; CCM, comprehensive care model; TNF, tumor necrosis factor.

Discussion

In the present study, the implementation of a CCM for the treatment of RA in a cohort of patients, showed an increase of 9.4% in the percentage of patients' adherence to subcutaneous anti-TNF treatment after 24 months of follow-up. During these months, individualized, multidisciplinary management was provided, focused on the patient's needs, guided by the clinical course of the disease, and actively involving the patient's participation.

For chronic diseases such as RA, adherence to treatment is a determining factor for achieving favorable outcomes in terms of health and quality of life.[18] However, the treatment continuity tends to be compromised by aspects of the health system, such as limited access to services, services fragmentation and restricted coverage.[19] On the contrary, some biopsychosocial factors related to greater adherence have been described, such as: adult age, female gender, married marital status, high income, resilience capacity, stable mental health, less disease activity, and knowledge about the disease.[8,9,19–23] This last characteristic does not only depend on the educational level, but the doctor–patient relationship also confers great influence on the patient's expectations regarding the management of the disease.[24] It also allows the resolution of doubts and fears, gives confidence, credibility, empathy, empowerment, participation in decision-making and construction of receptive, and effective communication strategies.[12,24,25]

It is important to highlight that there are different tools to evaluate adherence in rheumatology, particularly in RA patients; the CQR19, and the Medication Adherence Self-Report Inventory (MASRI),[26] questionnaires are the most extensively validated, but the CQR19 is long but precise and reliable tool, therefore we decided to use it. In fact, despite being a long questionnaire, it has been used as a self-administered survey to assess treatment adherence in patients with RA.[27] Also, the CQR19 has been used in different rheumatology settings when evaluating RA patients, as applied by rheumatologist, implemented in teleconsultation, and applied by nurses.[28–30]

On the other hand, the properties of treatment regimen, such as adverse events, dose, frequency, and route of administration, also influence adherence.[21,22] In this study, patients treated with Golimumab, administered monthly, showed greater adherence at the end of follow-up, unlike those treated with weekly (Etanercept) and every 2 weeks (adalimumab) administration regimens. Likewise, Bhoi et al[5] and Tkacz et al[31] found greater therapeutic adherence with Golimumab in patients with RA compared to other anti-TNF administered subcutaneously, which may be explained by its longer application interval, suggesting the existence of an inverse relationship between the frequency of each dose and treatment compliance. Moreover, similar results have been shown in a Spanish population, where patients using the monthly administration period had better adherence (assessed using the Medication Possession Ratio) than those using more frequent dosing schedules.[32,33]

To counteract the lack of adherence, various strategies have been recommended, such as: setting alarms and reminders, accessing digital programs, psychoeducational interventions to stimulate behavioral changes, and models

focused on motivating, leading to action and sensitizing thoughts and emotions.[21,34,35] Although, there have been numerous efforts, these tools have not shown a greater impact on adherence to RA treatment.[19]

Based on a new paradigm that seeks optimal clinical care, dynamic changes in treatment have been proposed based on strict control over the patient's symptoms and guided by pre-established therapeutic targets, called "treat to target", focused on achieving disease remission or low disease activity, leading to favorable long-term outcomes and improved quality of life.[6,36–39] A study carried out in Spain in which the medical records of patients with RA treated in 46 rheumatology units were audited,[32,33] found little implementation of strategies guided by therapeutic objectives in routine clinical practice. Only 4% of the patients had the level of disease activity evaluated monthly to adjust the formulated treatment. The foregoing warns of the possibility of lasting a longer time with high disease activity with its respective clinical implications and without treatment adherence due to not achieving remission and not undergoing rigorous clinical follow-up.[36] In contrast, the present results showed how a CCM impact positively on adherence in RA patients under subcutaneous anti-TNF treatment.

Currently, goal-guided therapeutic strategies are not available in all care centers, their institutionalization is limited by infrastructure, time availability, difficulty in scheduling appointments, higher costs, disuse of activity measurement indexes of the disease and lack of knowledge of patient-centered treatment alternatives.[6,36] The performance of protocolized treatment models oriented by therapeutic objectives in patients with RA has been evaluated to determine their effect on therapeutic adherence. Several studies have found an overall adherence between approximately 69% and 77%, which is also accompanied by effectiveness and usefulness compared to the standard treatment, given the number of patients in remission, the quality-adjusted life years and by decreased disease activity.[37,40,41] Regarding costs, despite an increase in these with the goal-guided model, in the long term, disease control and its lower progression would generate savings, due to less need to use health services.[42]

A holistic, non-fragmented, multidisciplinary management focused on the patient's well-being is the complement to goal-guided treatment to further increase adherence figures,[43] as demonstrated by the increase in adherence to the prescribed treatment and greater appointment adherence in the cohort of patients in this study. Therefore, comprehensive management of chronic diseases such as RA is a sustainable, feasible, and realistic strategy. In fact, Lesuis et al[44] demonstrated that a multicomponent intervention strategy, involving rheumatologists and nurses, can lead to improved adherence to tight control-based treatment and a reduction in the use of biologicals in RA.

This study has several weaknesses. This is a real-life cohort study, then we did not used a control group; therefore, we only described the adherence level of this group of RA patients under subcutaneous anti-TNFs therapy. Although cohort studies can be uncontrolled, with outcomes examined in a group of persons defined by a single characteristic, the design with subgroups being compared involves less biases.[45] Furthermore, we defined treatment adherence as a primary outcome under a CCM model and as a secondary objective, we evaluated its impact on disease activity, similarly to what has been done in other studies that evaluate adherence and concomitantly disease activity.[46–48] However, we recognize it is possible that there are other factors in the model that could influence on disease activity and that the final result is not only dependent on therapeutic adherence.

Also, there are additional limitations, one of which was that the study exclusively included patients treated with biological DMARDs (anti-TNF) administered subcutaneously. Considering biologics administered by other routes or different pharmacological groups for the treatment of RA, would have made it possible to explore associations between these with the implemented CCM. However, we decided to analyze this subgroup of patients, given that patients with subcutaneous anti-TNF treatment are the most frequent within the total group of patients treated with biological therapies in our country. Moreover, we recognize that some important variables like duration of disease and concomitant received DMARDs were not described nor analyzed, Additionally, we mention that the patients belong to the context of a reference institution, for which the results could not be extrapolated to the conditions of any center. On the contrary, it is considered a strength to have rigorously complied with the CCM follow-up for an important period of 24 months, to have used the CQR19 in its version validated and adapted in Colombia and to have adjusted the estimation of the effect by two clinimetric measurements widely used among these patients.[15]

Finally, the behavior of therapeutic adherence in the context of a CCM implemented in patients with RA demonstrates the value of adding to conventional pharmacological treatment and standard care, a set of strategies from a global and

comprehensive perspective that incorporates strict follow-up, monitoring activity level of the disease, monitoring of compliance with pre-established clinical goals, monitoring by professionals from different disciplines, therapeutic adjustment according to the patient's need, coverage and access facilities. The preceding to optimize patient care, benefiting their quality of life, favoring health outcomes and the ability to self-manage the disease.

Conclusion

The comprehensive care model implemented in a cohort of patients diagnosed with RA treated with anti-TNF drugs produced an increase in the percentage of adherent patients after 24 months of follow-up and stability over time in terms of the activity level of the disease and patient's physical function.

Data Sharing Statement

The authors declare that the database and other study materials are available for review at any time. All files, databases and other documents related to the study are available on electronic format with security protocols as requested by authorities. In any case, please contact PSM.

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Author Contributions

All authors 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.

Disclosure

PSM has received fees for conferences, counseling, advisory boards, and travel to academic meetings expenses and research grants in the last 5 years from Janssen, AbbVie, Biopass-UCB, Bristol, Lilly, Pfizer, Roche, Tecnofarma, and Sanofi. Dr Omar-Javier Calixto reports being a former employee of Janssen Cilag during the conduct of the study. Dr Adriana Rojas-Villarraga reports fees for conferences from AbbVie, from Amgen, from Biopas, from Bristol, from Janssen, from Pfizer, and fees for conferences and advisory board from Glaxo outside the submitted work. The other authors declare that they have no known competing commercial, financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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