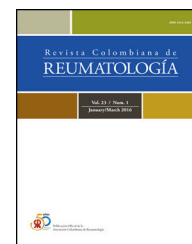




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Original Investigation

Early rheumatoid arthritis: Clinical and functional outcomes of a cohort treated in a high complexity hospital, Cali-Colombia[☆]



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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune multisystemic disease that affects the synovial joints. An appropriate and early management improves prognosis and course of the disease.

Objective: To evaluate the clinical and functional outcomes of patients with RA.

Methodology: Observational study with longitudinal follow up in a cohort of patients with early RA, with less than 12 months of evolution, classified according to the European League Against Rheumatism and American College of Rheumatology (ACR 2010) criteria. Remission criteria were taking into account according to Disease Activity Scale (DAS28-VSG), clinical activity disease index, and functional status according to Modified Health Assessment Questionnaire.

Results: The analysis included 99 patients with a mean age of 47.8 ± 15.5 years, and of which 92 (93%) were women. All patients were treated with synthetic disease-modifying antirheumatic drugs. At 3 months of follow-up, a significant decrease was observed in DAS28 scores and clinical activity disease index compared to the value at baseline values ($p < .05$). No significant differences were found between patients diagnosed before and after 3 months from onset of symptoms ($p > .05$).

Conclusions: A substantial improvement was observed in patients with early RA treated during first year from onset symptoms. Continuous and periodic monitoring of the pathology is an indispensable tool for evaluating disease progress and making adjustments in the therapeutic management.

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Artritis reumatoide temprana: resultados clínicos y funcionales de una cohorte en un centro de alta complejidad, Cali-Colombia

R E S U M E N

Palabras clave:

Artritis reumatoide temprana

Remisión

DAS28

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Introducción: La artritis reumatoide (AR) es una enfermedad crónica, inflamatoria, autoinmune y multisistémica, cuyo principal blanco es la membrana sinovial. El manejo adecuado y temprano mejora la evolución y pronóstico de la enfermedad.

Objetivo: Evaluar los resultados clínicos y funcionales en pacientes con AR temprana.

Metodología: Estudio observacional, con seguimiento longitudinal, de una cohorte de pacientes con AR temprana de menos de 12 meses de evolución, clasificados según los criterios de la Liga Europea Contra el Reumatismo y del Colegio Americano de Reumatología (ACR 2010). Se tuvieron en cuenta los criterios de remisión según la Escala de Actividad de la Enfermedad (DAS28-VSG) y el índice de actividad clínica de la enfermedad. Estado funcional según Cuestionario modificado de Evaluación de la Salud.

Resultados: Se analizaron 99 pacientes. La edad promedio de los pacientes fue de 47.8 ± 15.5 años, el 93% (92) eran mujeres. Todos los pacientes fueron tratados con fármacos anti-reumáticos modificadores de la enfermedad sintéticos. Durante el seguimiento a los 3 meses se observó una disminución significativa en los puntajes del DAS28 y actividad clínica de la enfermedad respecto al valor en la visita basal ($p < 0.05$). No se encontraron diferencias significativas en la evolución de pacientes diagnosticados antes y después de 3 meses desde el inicio de los síntomas ($p > 0.05$).

Conclusiones: Se evidencia mejoría sustancial de los pacientes con AR temprana tratados durante el primer año de inicio de los síntomas. El seguimiento continuo y periódico de la patología es una herramienta indispensable para evaluar el progreso de la enfermedad y hacer ajustes en el manejo terapéutico.

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune multisystemic disease that affects mainly the synovial membrane. RA is distributed worldwide, with higher prevalence in women¹ and in developed countries.² In Latin America, it has been reported a prevalence close to 0.5%.³ In Colombia, there are no accurate data on prevalence, although some approximations have been made with Afro-Colombian population, with an estimate of 0.4%.⁴

The definition of early RA varies according to the time of evolution. Some authors set as a time limit less than 3 months from the onset of the symptoms. However, for other authors this time can get to be up to 3 years.^{4,5}

The current treatment of RA is aimed at the remission, that is, to the absence of inflammatory activity, or at least to a significant reduction or a status of low disease activity.⁶ In the way to achieving this goal, patients should be closely monitored in their evolution, using different indicators that allow to assess the disease activity in order to determine the necessary modifications in the treatment and reach the expected outcome.

An adequate treatment, with periodic controls of the disease activity, improves the prognosis of RA. This has been focused on the concept of "goal-directed treatment" (T2T)

or targeted treatment, developed by a group of international specialists, which recommends having the goal of achieving the remission or low disease activity, through the systematic monitoring.⁷ The purpose of the present study is to evaluate the clinical and functional behavior of the patients with early RA, treated in the Clinic of Arthritis and Rheumatology of the Imbanaco Medical Center (CAR-CMI) and to characterize demographically and clinically this population.

Patients and methods

Type of study

Descriptive, longitudinal, case series study, which included patients between 18 and 65 years, who consulted to the CAR-CMI in the period 2004-2014, diagnosed with RA according to the criteria of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) EULAR/ACR 2010,⁸ with a time of evolution of symptoms shorter than 12 months, with at least one follow-up visit during the first year. Patients with diagnosis of fibromyalgia, systemic lupus erythematosus and other concomitant joint diseases such as gout and severe osteoarthritis were excluded, as well as those patients with major depression.

Place of study

The study was carried out at the CAR-CMI, a high complexity private health care provider institution, in the city of Cali, Colombia.

The evaluations were carried out periodically, as part of the routine clinical follow-up of patients. This study was approved by the Ethics Committee of the institution and all patients signed the informed consent form for the collection of information.

Variables

The demographic information was collected using a multi-dimensional questionnaire that included variables such as data of identification, gender, age, educational level marital status and socioeconomic stratum. The analytical variables were: rheumatoid factor, anti-cyclic citrullinated peptide antibody, antinuclear antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein and complete blood count. The clinical follow-up was carried out by means of DAS28-VSG (the Spanish version of DAS28-ESR), CDAI, MHAQ, global assessment of the disease activity by the patient and the physician, and visual analog scale for pain. In addition, the type of treatment used was documented.

The clinical remission was defined based on the DAS28-VSG with a cutoff point <2.6 . The EULAR response criteria were taken into account as follows: the good responders were patients who had a decrease in DAS28-VSG by at least 1.2 units with regard to the initial assessment: moderate response in those patients with a change between <1.2 and >0.6 units, and non-responders those who had changes ≤ 0.6 units.^{9,10} In the CDAI scale, it was considered a low disease activity when it was between 2.8 and 10.

As for the ACR response criteria, it was assigned a percentage of improvement of the number of swollen and painful joints and improvement in 3/5 of the following variables: global assessment of the disease activity by the patient and by the physician, AVS, MHAQ and ESR or C-reactive protein, giving different percentages with response at 20, 50 or 70%.¹¹

The modifications in the treatment of each patient were carried out according to the medical criteria of the rheumatologist, based on the above mentioned parameters. Clinimetric evaluations of the patients during the medical management were carried out approximately every 3 months. For this study, the evaluations of the patients were analyzed at 3, 6 and 12 months of follow-up. 85% of patients had information at 3 months, 58% at 6 months and 53% at one year.

Statistical analysis

A descriptive analysis was performed using frequency tables and measures of central tendency and dispersion, for qualitative and quantitative variables, respectively. Mixed-effect models for repeated measures were used for the comparison of the clinical (laboratory tests, DAS28-VSG, CDAI) and functional (MHAQ scale) outcomes through the follow-up and according to the time of evolution (<3 months). The models

were adjusted in the statistical software R.3.1.3, by restricted maximum likelihood estimation (REML).

Results

Study population

In the study period, 134 patients with early RA of less than one year of evolution were evaluated; of them, 99 patients who met the selection criteria were included; 35 patients were not included because they did not have a minimum evaluation at one year. The average age of the patients was 47.8 ± 15.5 years and 93% (92) were women. 85% of patients were diagnosed at ≤ 6 months from the onset of the symptoms and 46.6% of patients had less than 3 months of evolution.

Baseline evaluation

At baseline evaluation it was found that half of patients had between 3 and 12 painful joints. The anti-cyclic citrullinated peptide antibodies and the rheumatoid factor were positive in 77.8 and 77.5% of the subjects, respectively. In the DAS28-VSG scale, it was found that 38.8% had a moderate disease activity and 45.9% a high activity; the CDAI reported 37.3 and 48.4%, respectively. The treatment scheme and other clinical characteristics are summarized in [Table 1](#).

Treatment

The scheme of treatment was decided in the first visit of confirmation of the diagnosis and the first follow-up assessment was carried out about 3 months later. All patients received synthetic DMARDs, which included combined therapies with MTX, CQ/HCQ and SSZ. We only had knowledge of 2 patients who changed their treatment regime to leflunomide plus MTX after 7 and 18 months of follow-up and one patient who required biological therapy with etanercept at 31 months of evolution.

67% of patients received DMARDs combined with MTX plus CQ/HCQ during the first year. At 3 months of follow-up 27% of the patients received monotherapy with MTX or CQ/HCQ. Only 3% received triple therapy that included MTX, CQ/HCQ and SSZ.

At the first follow-up visit, 65% of patients were treated with steroids at doses lower than 15 mg, at one year of follow-up 45% of the patients evaluated continued with steroids at doses less than or equal to 5 mg. At the third month, 22% of patients were managed with anti-inflammatory agents, decreasing to 4.7% in the first year.

Follow-up

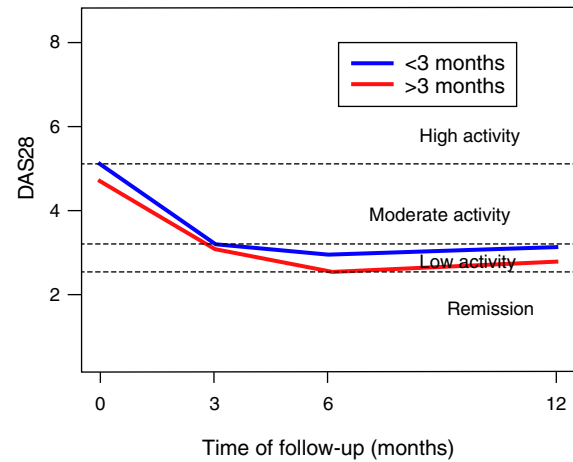
At the time of the diagnosis, the patients had an average ESR of 29 mm/h, with a decrease of 8 mm/h at 3 months and one year of follow-up ($p < 0.05$). The evaluation of the global disease activity performed by the physician (4.4 ± 2.4), reported lower values compared with those reported by the patient (5.1 ± 2.4), in the baseline visit. A reduction in the score of the global disease activity was found during the follow-up,

Table 1 – Baseline characteristics of the patients.

Variables	N = 99
Clinical characteristics	
Age	
Mean±SD	47.8±15.5
Gender n (%)	
Female	92 (92.9)
Months of evolution of the disease	
Median (IQR)	4.0 (2.0–6.0)
Evolution <3 months n (%)	46 (46.5)
Months of follow-up	
Median (IQR)	12 (3–35)
Number of controls	
Median (IQR)	3 (2–4)
Number of painful joints	
Median (IQR)	8 (3–12)
Number of swollen joints	
Median (IQR)	3 (0–8)
Global activity by physician	
Mean±SD	4.4±2.4
Global activity by patient	
Mean±SD	5.1±2.4
DAS28 (n = 74)	
Mean±SD	4.8±1.4
CDAI	
Mean±SD	22 (14–29)
EVA	
Mean±SD	6.0±2.9
MHAQ	
Mean±SD	0.8 (0.3–1.3)
Drugs at the baseline assessment	
NSAIDs	59 (59.6)
Steroids	25 (25.2)
Methotrexate (MTX)	7 (7.1)
CQ/HCQ	16 (16.2)
SSZ	1 (1.0)
Paraclinical characteristics	
Hemoglobin (n = 84)	
Median (IQR)	13.3 (12.3–14.1)
ACCP n (%)	
Positive (n = 77)	77 (77.8)
Rheumatoid factor n (%)	
Positive (n = 89)	69 (77.5)
Antinuclear antibodies n (%)	
Positive (n = 66)	6 (9.1)
CRP (n = 67)	
Positive, median (IQR)	41 (61.2), 24.0 (14.4–41.5)
ESR	
Median (IQR)	26.5 (10.0–38.7)

based on what was reported by the physician and the patient ($p < 0.05$). However, only the scores determined under medical criterion varied significantly between the patients diagnosed before and after 3 months of evolution, finding a greater disease activity in the patients diagnosed in the first trimester ($p < 0.05$).

In the DAS28-VSG scale, it can be observed a significant change in the scores during the follow-up ($p < 0.001$), with a reduction in 1.5 points at 3 months, of 1.9 at 6 months, and of 1.6 at one year of follow-up (Fig. 1). The CDAI scale, as well as the DAS28-VSG scale, indicates a significant decrease in the disease activity in the patients ($p < 0.05$).

**Fig. 1 – DAS28 scale over the follow-up time.**

No differences in the ESR values were found in the global assessment of the disease by the patient and in the DAS28-VSG scale, in the patients diagnosed before 3 months of evolution. The data suggest higher scores on the CDAI scale in the patients diagnosed in the first trimester of evolution of the disease ($p: 0.056$).

The activity of the disease, classified according to the DAS28-VSG and CDAI scales, is shown in Table 2. In the third month, it was found that one out of 3 patients was in remission of the disease, according to the DAS28-VSG scale. A decrease in the proportion of patients with high disease activity is observed in both scales through the follow-up.

The functionality of the patients, assessed by the MHAQ, showed a statistically significant improvement ($p < 0.05$) in the first year of follow-up. The foregoing suggests that patients intervened for the control of their disease, are able to improve their quality of life in the performance of daily activities, such as getting dressed, eating, walking, among others. No changes in the functionality of the patients were observed in the MHAQ scores over time, in the patients diagnosed before and after 3 months of evolution (Fig. 2).

Response to treatment

For the evaluation of the response to treatment, the patients were classified according to the EULAR response criteria. It was

Table 2 – Percentage of remission (DAS28 < 2.6) and (CDAI ≤ 2.8).

	Basal	3 Months	6 Months	12 Months
DAS28 (N)	77	72	51	47
Remission (<2.6)	7.8%	33.3%	47.1%	38.3%
Low (≤3.2)	7.8%	15.3%	21.6%	25.5%
Moderate (>3.2 to ≤5.1)	37.7%	44.4%	29.4%	21.3%
High (>5.1)	46.7%	6.9%	1.9%	14.9%
CDAI (N)	99	83	58	53
Remission (≤2.8)	3.0%	21.7%	25.9%	22.6%
Low (>2.8 to ≤10)	11.1%	44.6%	50.0%	43.4%
Moderate (>10 to ≤22)	37.4%	21.7%	13.8%	24.5%
High (>22)	48.5%	12.0%	10.3%	9.4%

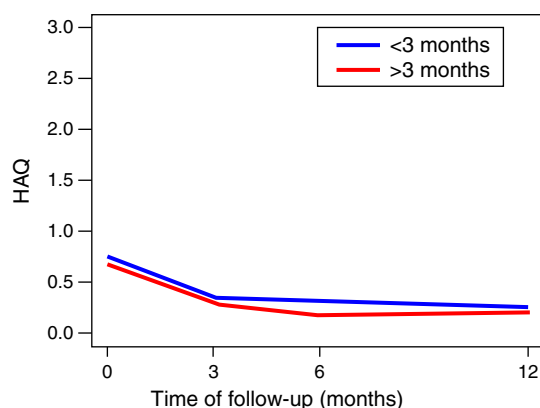


Fig. 2 – HAQ scale over the follow-up time.

found that at 3 months of follow-up, 32% were good responders, 48% moderate responders and, 20% non-responders to treatment. By the ACR criteria 20, 50 and 70, at 3 months of treatment it was found a response of 72.8, 45.7 and 22.2%, respectively. 35% of the patients who did not respond to treatment withdraw the medications before completing the management, causing relapses and reactivation of the disease.

Discussion

In this study, it was found that the demographic characteristics of the population with RA do not differ from those reported in previous national and international studies. It was observed a predominance of the disease in women¹²⁻¹⁴ and in people older than 45 years.^{1,15}

Our data suggest that the remission of the disease is achieved in around 3 months, with similar results at one year of follow-up, as evidenced with the DAS28-VSG and CDAI scales. This is an important finding, since the control of the disease for prolonged periods entails less joint destruction, and an improvement of the functionality and of the quality of life. These findings are similar to those reported by other authors,¹⁶⁻¹⁸ but lower than those indicated in the TICORA study.¹⁹ We found no differences in the evolution of the patients who were diagnosed during the first trimester from the onset of the symptoms. The foregoing differs from that reported by other authors who have considered that the very early diagnosis and management (<3 months) of the disease is related to better outcomes.^{16,20}

The evaluations carried out demonstrate the effectiveness of the management of the disease before 12 months, according to the therapeutic response as stated by EULAR and ACR. Currently, it is considered that treatment with disease-modifying drugs confers a significant advantage in the management of RA²¹ and even more, if it has been started early, improving the functional response and the quality of life.^{17,22,23}

The initial treatment of the patients with RA managed in the CAR-CMI, consists in the use of steroids as bridge therapy, starting with intermediate doses, which are progressively reduced over time according to the therapeutic effect of the DMARDs. Although an evaluation of the patient response

according to the type of therapy used was not carried out in this study, our results show an improvement of the patients that can be attributed to the initial treatment. Different studies have demonstrated the efficacy of low-dose steroids together with DMARDs in RA of less than 2 years of evolution.²⁴⁻²⁶ The combination of these drugs has shown to reduce the symptomatology, improve the functional prognosis of the patients, reduce the radiological progression and likewise reduce the need for biological therapy to achieve clinical remission.

The therapeutic management with DMARDs was provided to the patients based on the International^{27,28} and Latin American^{4,29} guidelines. These guidelines support the early use of the DMARDs as first-line treatment and of the biological agents as second-line treatment. This is because the biological therapy may entail a greater cost for the patient and is reserved for those who have persistent active disease and do not respond to conventional combinations. We only had information that 1% of patients required management with biological therapy, after 3 years of follow-up. The foregoing suggests a control of the early disease with the conventional DMARDs. However, this percentage may be higher, due to the great number of losses to follow-up. It is important to highlight that the biological medicines are effective. Nevertheless, the need for a long-term treatment and their toxicity can make them less cost-effective and increase the direct costs related to the drugs.^{30,31} While what it matters is the control of the disease with the use of available therapies, the economic analyses support the concept of therapies with DMARDs and the rapid stepping of treatment when there is an insufficient response, seeking alternatives that generate cost-benefit both for patients and for the healthcare system, this concept goes hand in hand with the current recommendations of EULAR which are consistent with the rational use of the resources of the society.³²

It is important to mention that the la CAR-CMI has a special educational program for patients with RA, which contains educational videos, lectures for patients, accompaniment in rehabilitation by physical therapy, occupational therapy and personnel trained for the integral treatment of the pathology, which seeks to guide the patient in the management of his disease and to achieve a greater adherence to the proposed treatments. This is supported by previous studies that evaluated the role of patients' education, which provides additional benefits for the management and control of the disease.^{33,34} Despite all patients entered in the education program, one-third had relapses due to treatment interruption.

This study represents the real life in clinical practice. The treatments were planned and adjusted according to the disease activity, count of swollen and painful joints, functionality, comorbidities and tolerability of the treatment. Since the data come from the clinical follow-up carried out during the medical management of the patients in the CAR-CMI and they were not strictly collected for this study, there may exist problems in the quality of the information and in some cases it was not possible to obtain the follow-ups of the clinical and functional variables in the first year of follow-up.

On the other hand, a standardized treatment for the group was not established as in other protocols, however, these data may reflect the management given to patients in clinical practice.

Conclusions

A substantial improvement of the patients with early RA treated during the first year after onset of symptoms is evidenced. The continuous and periodic follow-up of the pathology is an indispensable tool to assess the progress of the disease and make adjustments in the therapeutic management, which leads to alter the course of the disease and improve the quality of life.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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Conflict of interest

The authors declare they did not have any conflict of interest at the time of the writing of the manuscript.

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REFERENCES

1. Guías prácticas para el tratamiento de la artritis reumatoide. Bogotá: Asociación Colombiana de Reumatología; 2007.
2. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther*. 2009;11:229.
3. Delgado-Vega AM, Martín J, Granados J, Anaya JM. Genetic epidemiology of rheumatoid arthritis: what to expect from Latin America? *Biomedica*. 2006;26:562-84.
4. Guía de práctica para la detección temprana, diagnóstico y tratamiento de la artritis reumatoide. Bogotá, Colombia: Ministerio de Salud y Protección Social-Colciencias; 2014. p. 1-95.
5. Demoruelle M, Deane K. Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid arthritis. *Curr Rheumatol Rep*. 2012;14:472-80.
6. Anaya J, Pineda-Tamayo R, Gómez L, Galarza Maldonado C, Rojas-Villarraga A, Martín J. Artritis reumatoide. Bases moleculares, clínicas y terapéuticas. Medellín: Corporación para Investigaciones Biológicas; 2006.
7. Katchamart W, Bombardier C. Systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis. *J Rheumatol*. 2010;37:1411-5.
8. Aletaha D, Neogi T, Silman AJ, Funovitis J, Felson DT, Bingham CO III, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;62:1580-8.
9. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken)*. 2012;64:640-7.
10. van Gestel a M, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum*. 1996;39:34-40.
11. Felson DT, Anderson J, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 1995;38:727-35.
12. Nienhuis RL, Mandema E. New serum factor in patients with rheumatoid arthritis; the antiperinuclear factor. *Ann Rheum Dis*. 1964;23:302-5.
13. Avila Portillo L, Londoño-Patiño J, Cardona A, Salazar Uribe J, Santos AM, Romero Sánchez C, et al. Valores de referencia de los anticuerpos anti-citrulina IgG, e isotipos IgG e IgA del factor reumatoide en un grupo de individuos del Hospital Militar Central. *Rev Colomb Reumatol*. 2014;11:201-8.
14. Correa P, Tobón J, Citera G, Cadena J, Schneeberger E, Camargo JF. Anticuerpo Anti-PCC en Artritis Reumatoide: Relación con características clínicas, citocinas T1/T2 y HLA-DRB1. *Biomédica*. 2004;140-52.
15. Rantapää-Dahlqvist S, De Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum*. 2003;48:2741-9.
16. Gremese E, Salaffi F, Bosello S, Ciapetti A, Bobbio-Pallavicini F, Caporali R, et al. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis*. 2013;72:858-62.
17. Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Llonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination - disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum*. 2002;46:894-8.
18. Verstappen SMM, Jacobs JWJ, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer assisted management in early rheumatoid arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis*. 2007;66:1443-9.
19. Grigor C, Capell H, Stirling A, McMahon A, Lock P, Vallance R. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single blind randomised controlled trial. *Lancet*. 2004;354:263-9.
20. Nell VPK, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy

- with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology*. 2004;43:906-14.
21. Wilske KR, Healey LA. Remodeling the pyramid – a concept whose time has come. *J Rheumatol*. 1989;16:565-7.
 22. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis*. 2002;61:290-7.
 23. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update – American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. *Arthritis Rheum*. 2002;46:328-46.
 24. Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2007:1-2.
 25. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2012;156:329-39.
 26. García-Magallón B, Silva-Fernández L, Andreu-Sánchez JL. Update on the use of steroids in rheumatoid arthritis. *Reumatol Clin*. 2013;9:297-302.
 27. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis*. 2010;69:964-75.
 28. Saag KG, Gim GT, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Care Res*. 2008;59:762-84.
 29. Actualización de las guías de práctica clínica en el tratamiento de la artritis reumatoidea. Buenos Aires: Sociedad Argentina de Reumatología; 2013.
 30. Kavanaugh A. Health economics: implications for novel antirheumatic therapies. *Ann Rheum Dis*. 2005;64 Suppl. 4:iv65-9.
 31. Montoya N, Gómez L, Vélez M, Rosselli D. Costos directos del tratamiento de pacientes con artritis reumatoide en Medellín, Colombia. *Rev Colomb Reumatol*. 2011;18:26-33.
 32. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewe R, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:995-1003.
 33. Escorcía ME, Osorio HJ, Pérez CA, Thulcán MC, Caballero CV, Borda M. Efectividad de una intervención educativa en pacientes con artritis reumatoide. Hospital Universidad del Norte. Barranquilla. Abril-Mayo de 2005. *Rev Colomb Reumatol*. 2006;13:11-9.
 34. Riemsma RP, Kirwan JR, Taal E, Rasker JJ. Patient education for adults with rheumatoid arthritis. *Arthritis Rheum Cochrane Database Syst Rev*. 2003:CD003688.