

Distinct pattern of rheumatoid factor serotypes in serial evaluation of patients with early rheumatoid arthritis

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ABSTRACT

Introduction: Rheumatoid factor (RF), despite its limitations, is still the most applied serological marker for diagnosis of early rheumatoid arthritis (RA). Sensitivity, specificity, correlation with prognosis and radiological progression, as well as variation over time of serotypes titers IgG, IgM and IgA, are yet controversial. **Objective:** To evaluate the pattern of the different RF serotypes (IgG, IgM, and IgA) in serial evaluations during the first 36 months after RA diagnosis and their correlation with occurrence of radiographic erosions. **Patients and methods:** Forty patients with diagnosis of RA (less than 12 months of symptoms) were evaluated during 3 years of follow-up. Titers of RF serotypes were analyzed by ELISA at the initial evaluation and after 12, 24 and 36 months of follow-up. A mixed-effect regression model was applied, considering the presence of radiographic erosions as outcome (annual radiography of hands and wrists, feet and ankles). **Results:** At the initial evaluation, 30%, 42.5% and 50% of the patients were positive for IgG, IgA and IgM RF, respectively. The titers of IgA and IgM RF were higher for patients who had radiographic erosions during the follow-up period (10-220 IU/dL *versus* 0 to 10 IU/dL in patients without erosions, $P < 0,05$). The titers of IgM and IgG RF remained unchanged over the three years of follow-up. On the other hand, there was a positive linear increasing trend for titers of IgA RF ($P = 0.0013$) only in the group with radiographic erosions. **Conclusion:** 1) Search of RF serotypes IgA and IgG does not increase the frequency of RF positivity and therefore it does not contribute to the RA diagnosis; 2) IgM RF stability observed over time does not justify repeated requests of RF during RA follow-up; 3) higher titers of IgA and IgM RF are observed in more severe patients, with radiographic erosions; 4) IgA RF presents a clearly distinct behavior in patients with or without radiographic erosions, which may have implications for pathophysiology and prognostic evaluation of the disease.

Keywords: rheumatoid factor, serotypes, early rheumatoid arthritis, diagnosis, prognosis.

INTRODUCTION

In the last decades, there has been a significant evolution in the knowledge of rheumatoid arthritis (RA) physiopathogeny, leading to changes in disease's approach and therapeutics. The concept of "early or initial rheumatoid arthritis" was defined by the majority of authors as the initial phase of disease symptoms up to 12 months, period of time in which

establishing of adequate therapy would result in increased clinical improvement. It has also been possible to confirm that early treatment and diagnosis can modify the disease course.¹ Laboratorial and image methods were developed, contributing to an earlier diagnosis and prognostic determination,² and, above all, there have been great changes in therapeutic approach of the disease, with the use of novel classes of drugs.³

Received on 11/03/2008. Approved on 02/18/2009.

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Despite the description of new diagnostic and prognostic markers for RA, most of all in its early phase, rheumatoid factor (RF) is still the most used serological marker for early RA diagnosis.⁴

RF is found in about 70% of patients with established RA, and it is of great importance for the diagnosis and prediction of disease prognosis.⁴ The presence of RF is one of the seven 1987 classification criteria of the American College of Rheumatology (ACR)⁵ and its detection is variable according to the dosage method and to the isotype.⁴ Only the IgM isotype is examined in routine tests.

RF, nevertheless, presents a series of limitations as a marker for RA initial phase diagnosis:⁴ there is controversy regarding sensitivity, specificity, correlation with radiographic prognosis and variation over time of usually investigated serotypes titers – IgG, IgM and IgA.

The objective of this work was to examine the pattern of different RF serotypes (IgG, IgM, and IgA), in serial evaluations over 36 months, and its correlation with the occurrence of radiographic erosions, in a large group of patients with early RA diagnosis.

PATIENTS AND METHODS

As a prospective observational study, measurements of IgA, IgG and IgM RF were registred over time (36 months) in patients with early RA diagnosis.

Forty patients were evaluated with early RA diagnosis. They were followed up in the *Clínica de Artrite Reumatoide Inicial do Hospital Universitário de Brasília* over three years and included in the study consecutively.

Initial RA was defined as the occurrence of articular symptoms compatible with the disease, lasting more than 6 weeks and less than 12 months. The criterion used was the clinical diagnosis of RA, performed by the rheumatologist, independently of the ACR classification criteria fulfillment.

Titration of RF serotypes (IgG, IgM, and IgA) was performed by ELISA⁶ (Quanta lite of INOVA Diagnostics Inc.), in baseline and serially over 36 months (evaluations in 3, 6, 12, 18, 24, and 36 months). The detection test was semiquantitative, and values superior to 15 IU/mL (RF IgM and IgA) and 20 IU/mL (RF IgG) were considered as positivity cut off.

Simple radiographies of hands and wrist, feet and ankles were performed annually (in baseline and at 12, 24, and 36 months), and the reports were issued by only one radiologist, who did not know the results of the patients' serologies and the sequence of the tests. The report was about the presence or absence of erosion.

During the whole follow-up, patients received the standard treatment protocol used in the service, including traditional disease-modifying antirheumatic drugs (DMARDs) and/or biological therapy, according to necessity.

For the purpose of analysis, a regression model of mixed effects was applied, considering as outcome the occurrence of radiographic erosions and using the following statistic model:

$$y_{ijk} = \mu + \alpha_i + b_{ij} + \gamma_k + (\alpha\gamma)_{ik} + \varepsilon_{ijk}$$

where: y_{ijk} is the measure of the titers IgA, IgG or IgM RF in k time, over the j th patient from group i

$\mu + \alpha_i + \gamma_k + (\alpha\gamma)_{ik}$ is the mean of the titers of IgA, IgG or IgM RF from group i in k time

b_{ij} is the random effect associated with the patient j in group i , $N(0, \sigma_B^2)$

ε_{ijk} is the random error associated with the patient j from group i in k time, with variance and covariance matrix with random intercept (RI).

We chose to use this new statistic model, mixed effects regression, for it is a study in which the longitudinal data present a hierarchic structure (repeated measures for the same individual). The mixed effects regression model allows the analysis of unbalanced longitudinal data (measures obtained in each individual observed in different times) in hierarchical structure, incorporating the dependency and the structure of errors correlation.

The significance level of 5% was considered.

The work was approved by the *Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de Brasília*.

RESULTS

Characteristics of the studied population

Among the 40 patients followed-up with early RA diagnosis, there was a predominance of female gender (36 patients, 90%) and the mean age was 45.9 years (21 to 71). The mean duration of articular symptoms in the moment of diagnosis was 20.8 weeks (4 to 48), and 19 patients (47.9%) had less than 12 weeks of symptoms before the diagnosis. Although the fulfilling of ACR criteria has not been considered as definition criterion of initial RA in this study, 33 patients (82.5%) fulfilled at least four ACR criteria in the first evaluation, and 100% after 12 months. Most patients (34 individuals, 85% of the sample) had not received previous treatment for RA until the moment of the initial evaluation.

There was no loss of follow-up of any patient during the three years of the study.

Presence of radiographic erosions

At baseline, 17 patients (42.5%) presented at least one erosion in the radiographs of hands and wrist, feet and ankles. During follow-up, there was a change in this percentage (Figure 1), so that, after 36 months of follow-up, 28 (70%) patients presented at least one erosion.

Pattern of the different serotypes of RF (IgG, IgM, and IgA), in the serial evaluations, and correlation with occurrence of radiographic erosions

At baseline, 21 patients (52.5%) were positive for at least one of the RF serotypes – 17 patients (42.5%) for IgA RF, 12 (30%) for IgG RF, and 20 (50%) for IgM RF, respectively. Sixteen patients (40% of the total sample and 76.1% of those positive for at least one of the RF serotypes) were positive for more than one serotype. Just two patients (5% of the total) were negative for IgM RF and positive for IgA RF.

Profile descriptive analysis per group

The pattern of IgA, IgG and IgM RF was analyzed over time (months) according to the presence or absence of erosion, as demonstrated in Figure 2.

Among those patients with “present erosion” in the initial moment or over the evolution (28 individuals), 18 (64.2%) were positive for at least one serotype of RF in the initial evaluation – 15 (53.5%) being positive for IgA RF, 8 (28.5%)

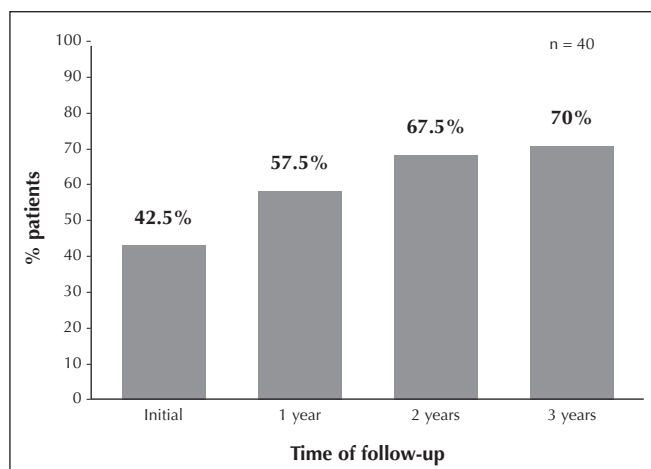


Figure 1. Evolution of radiographic erosions profile – occurrence of at least one radiographic erosion (radiograph of hands and wrists, feet and ankles) in initial evaluation and serial follow-up.

for IgG RF, and 17 (60.7%) for IgM RF. Sixteen patients (57.1% of the total of patients with present “erosion”) were positive for more than one RF serotype.

In the “absent erosion” group during follow-up (12 individuals), three patients (25%) presented initially positive RF. In one of the cases, only the IgA serotype was found, and in the others the three serotypes of RF were present.

As shown in Figure 2 (descriptive analysis), a uniform distribution in the titration of IgA, IgM and IgG RF (from 0 to 10 IU/mL) was observed in patients of “absent erosion” group, exception made to two cases that presented values of all of the RF isotypes above that level (from 0 to 10 IU/mL) and to one individual who presented values of IgG RF discrepant from the group.

In the “present erosion” group, the titers of IgA RF and IgG RF ranged from 10 to 200 IU/mL (Figures 2A and 2B) and the IgM RF ones varied from 10 to 220 IU/mL (Figure 2C). The IgA and IgM serotypes presented values statistically superior to patients in “absent erosion” group ($P < 0.05$ for both).

Analysis of estimated tendency compared to observed means

To better evaluate the pattern of RF serotypes over time, in relation to the occurrence of radiographic erosion, the adjusting of estimated tendencies model was done compared to means observed in the titers of IgA, IgG and IgM RF by group (“absent erosion” *versus* “present erosion”), over 36 months of follow-up, as shown in Figure 3.

For the IgA RF (Figure 3A), the model adjustment revealed that the linear effect for “absent erosion” group was not significant ($P = 0.8048$), while for “present erosion” group there was a significant linear tendency ($P = 0.0013$); the titers of IgA RF tended to increase over time in patients who presented erosions. The difference between titers of IgA RF of the two groups was statistically significant in all periods analyzed, except in the 12 months analysis, due to one isolated (discrepant) value of a patient who lowered the mean for the group with erosion.

In the case of IgG RF (Figure 3B), the pattern of behavior was similar for patients with or without radiographic erosion and the linear effect was not significant ($P = 0.2007$ and $P = 0.5833$, respectively), it represents the mean values of IgG RF tend to vary very little over time in patients with or without erosion. There was not statistic difference ($P > 0.05$) regarding the titers of RF IgG in the two groups (presence and absence of radiographic erosions) during the 36 months of follow-up.

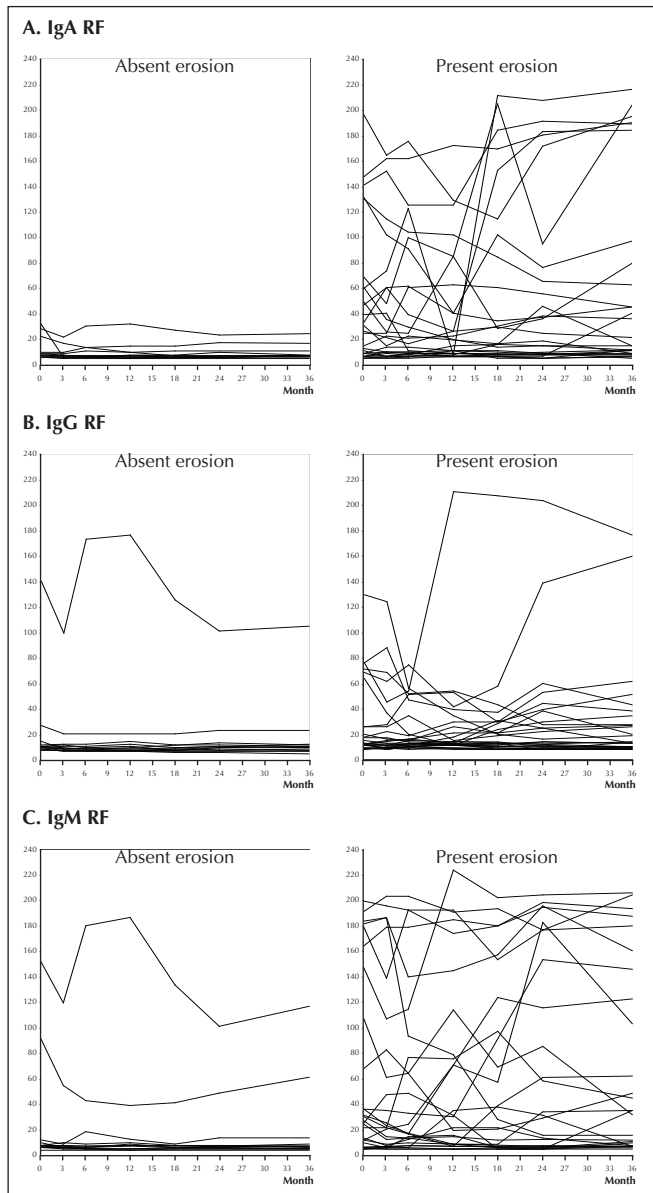


Figure 2. Chart of model adjustment of estimated tendencies compared to observed means in the titers of rheumatoid factor (RF) IgA, IgG and IgM per group (“absent erosion” versus “present erosion”), over 36 months of follow-up. For IgA RF (Figure 3A), the model adjustment reveals that the linear effect for “absent erosion” group is not significant ($P = 0.8048$), while for “present erosion” group there is a significant linear tendency ($P = 0.0013$), it means that IgA RF titers tend to increase over time. The difference between the two groups is significant ($P < 0.05$) in all periods analyzed, except in the analysis of 12 months. In the case of IgG RF (Figure 3B), the behavior pattern is similar for patients with or without radiographic erosion: the linear effect is not significant ($P = 0.2007$ and $P = 0.5833$, respectively), which represents mean values of IgG tend to vary very little over time. The model adjustment for IgM RF (Figure 3C) also shows that, for the group of patients without erosion, mean values of IgM RF tend to vary very little over time ($P = 0.4728$), while for the group with erosion there is a positive, almost significant tendency of linear effect ($P = 0.0568$). The difference between IgM RF titers of the two groups is significant ($P < 0.05$) from the 12th month of follow-up. (Regression of mixed effects analysis).

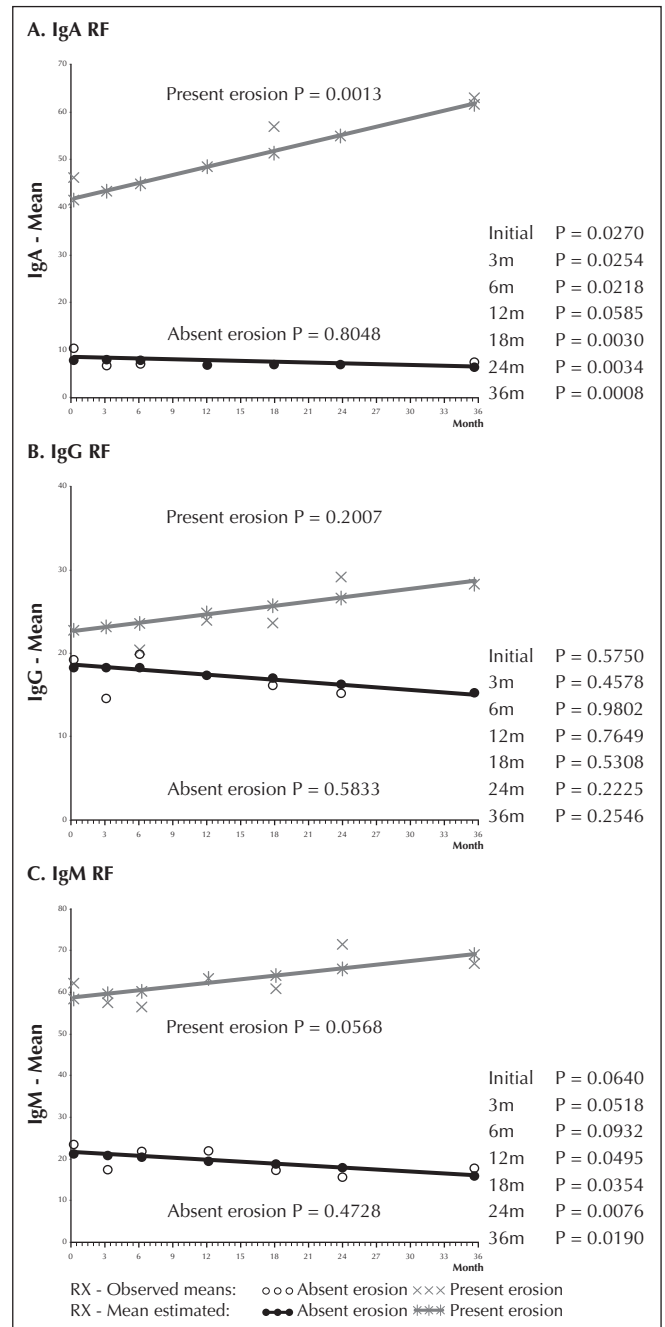


Figure 3. Chart of profile per group – behavior of patients over time (months – m) in relation to measurements of rheumatoid factor (RF) IgA, IgG and IgM per group (“absent erosion” versus “present erosion”). It is observed that the patients of “absent erosion” group are uniformly distributed regarding the titration of IgA, IgM and IgG RF (from 0 to 10 IU/mL), while in the “present erosion” group patients presented different behaviors regarding the titration of RF. The titers of IgA RF (Figure 2A) varied from 10 to 200 IU/mL, and values superior to the patients in the absent erosion group were presented. The IgG RF titers (Figure 2B) also ranged from 10 to 200 IU/mL in the “present erosion” group, but did not tend to present superior values in relation to “absent erosion” group. The IgM RF titers (Figure 2C) varied from 10 to 220 IU/mL in patients with erosions presenting superior values in relation to patients without erosion. (Descriptive analysis).

The model adjustment for IgM RF (Figure 3C) also shows that for the group of patients without erosion, mean values of IgM RF tend to vary very little over time ($P = 0.4728$), while for the group with erosions, there is a positive tendency of linear effect, almost significant ($P = 0.0568$). Starting from the 12th month of follow-up, the difference between the titers of RF IgM of the two groups is significant ($P < 0.05$).

DISCUSSION

The validity of the RF isotypes research in the evaluation of initial RA remains questionable. For example, the existence of correlation between the titers of different isotypes of RF and the diagnosis of RA is not defined, as well as the relation between the presence of some specific serotype (or more than one) and a worst radiologic prognostic, or the behavior of different RF isotypes over time.

Although there is controversy, it was suggested IgM, IgA and IgG RF are significantly associated to RA diagnosis.⁴ The isotypes positivity seems to be variable according to the studied population.⁸ In the work by Visser *et al.*,⁹ ELISA sensitivity for IgG, IgA and IgM RF was 72%, 44%, and 69%, respectively, and the specificity was 52%, 84%, and 86%. The metaanalysis of Nishimura *et al.*¹⁰ concludes that, for IgM RF, sensitivity and specificity (with the respective confidence intervals – CI) were 69% (CI: 65% to 73%) and 85% (CI: 82% to 88%). The results for RF IgG and IgA were similar.

In our study, IgM RF was observed in 49,23%, IgA in 43% and IgG in 29,2% of the patients with RA diagnosis and less than 12 months of symptoms duration – rates similar to the ones referred in other works, such as the one by Vittecoq *et al.*,⁸ which described the presence of IgM RF in 51%, IgA RF in 36% and IgG RF in 32% of the patients with RA diagnosis and less than two years of duration.

IgM RF is a useful marker for discriminating patients with polyarthritis who will evolve or not to RA.^{8,11-14} On the other hand, diagnostic properties of IgA and IgG RF are questioned.^{8,12,15,16,17}

Some authors have reported conflicting results regarding the fact that IgG and IgA RF are possible better prognostic markers than IgM RF for RA.¹⁸⁻²² In the metaanalysis of Nishimura *et al.*,¹¹ greater differences between the three serotypes were not found.

Rantapää-Dahlqvist *et al.*⁶ demonstrated in blood samples obtained before the beginning of RA (blood donors) that the presence of the three serotypes, especially IgA RF, was a predictor of RA. IgA and IgM RF were detected in serum stored to 18 years before the diagnosis of RA.¹⁹

In our study, the search of RF serotypes IgA and IgG did not increase the frequency of RF's positivity; therefore, it did not seem to contribute to initial RA diagnosis.

RF is known as one of serologic markers associated to a worst prognostic in RA,²⁰ including a serious radiological evolution of the disease.²¹⁻²⁴ On the other hand, the studies are not as clear regarding the importance of other RF isotypes as predictors of the occurrence of erosion in patients with early RA diagnosis.

Di Franco *et al.*²⁵ correlated the levels of RF IgA, IgG and IgM with the occurrence of erosions at magnetic resonance, but not in plain radiographs. Visser *et al.*⁹ demonstrated that the specificity of all RF isotypes in the discrimination between nonerosive or erosive RA after two years of evolution was low (RF IgG: 41%, IgA: 44%, and IgM: 47%) and that the IgG and IgA isotypes were not useful for diagnosing RA and predicting erosive disease.

Most authors agree that the presence of RF IgM is an independent predictor of the occurrence of radiographic erosion.^{26,27} Other works suggest that elevated serum concentrations of RF IgA can be an early and reliable marker of evolution to erosive forms of RA.^{28,29} Elevated titers of RF IgG have also been considered determinative of a worst radiographic prognosis.²⁷

Regarding the possible association between the RF serotypes titers and the radiologic prognostic, our results demonstrated that, in a purely descriptive analysis higher titers of the three serotypes are observed in critical patients, with radiographic erosions. Nevertheless, over the follow-up, only the most elevated mean values of RF IgA (since the first evaluation) and RF IgM titers (from the first year of follow-up) are statistically correlated to the occurrence of erosions. The presence of IgG RF could not predict the occurrence of the erosive form of RA neither on the initial moment nor during the follow-up.

Regarding the behavior of different RF isotypes titers over time, we tried to determine if the variations in its titers could predict a better or worse radiographic prognosis.

Variations in the titers of different RF isotypes during the patients with RA follow-up were observed, especially in works evaluating the influence of specific therapeutics over RF titers.^{16,30-32}

Swedler *et al.*¹⁶ demonstrated that there was a continuous decline of the three RF serotypes in patients being treated with gold salts. Previously, Lemm *et al.*³⁰ had published that the titers of IgG RF seemed to be a good parameter for the evolution of RA control under therapy with gold salts.

Bobbio-Pallavicini *et al.*³¹ observed that in patients being treated with infliximab, although the proportion of positive

individuals for RF stabilizes over time, the mean of RF titers suffers a progressive reduction. The same authors later reported that, in patients using infliximab and DMARDs, the treatment resulted in an early and significant reduction of the RF IgA and IgM titers, but not RF IgG, and the decrease of IgM was sustained.³²

On the other hand, we observed in our work that RF IgA showed a clearly distinct evolutive behavior in patients who presented or not radiographic erosions, which had not been previously reported. RF IgA titers increased over time among patients who presented erosions and stabilized in the remaining, although both groups have received treatment with DMARDs since the early diagnosis, including biological therapy.

The behavior of RF IgM was similar to RF IgA, but there was not statistic significance. Maybe the increase of the studied casuistic or of the time of follow-up allows greater conclusions about the matter. The titers of RF IgG did not suffer variation over time.

These changes in RF titers during patients follow-up have a yet uncertain meaning. It is possible that the increase in RF IgA titers during the three years of follow-up, observed only in patients who presented radiographic erosions, is a marker of bad prognostic in a population with severe evolution. The presence of radiographic erosions evolved from 42,5% in the initial evaluation to 70% in the third year, despite early treatment (47,9% of the patients begun follow-up and treatment with up to 12 weeks of articular symptoms).

This behavior of RF IgA, distinct of the remaining serotypes, can have possible implications in the physiopathogenesis and in the prognostic evaluation of the disease.

Due to the limited number of individuals evaluated, and to the various subschemes of treatment used, it was not possible to evaluate the influence of DMARDs use over the radiographic evolution. It is known that the early use of the adequate therapy for RA, whether it is conventional or biological, could inhibit the appearance of erosions. This could be a factor of confusion in the evaluation of radiographic evolution outcome in the evaluated population in this study.

CONCLUSIONS

The results of this work allow us to conclude that:

- 1) RF IgA and RF IgG serotypes research does not increase the positivity frequency of RF and, therefore, does not contribute to diagnosis of RA;
- 2) RF IgM stability observed over time does not justify repeated solicitations of RF during RA evolution;

- 3) Higher titers of the three serotypes are observed in critical patients with radiographic erosions, but only the most elevated mean values of RF IgA (since the first evaluation) and RF IgM titers (from the first year of follow-up) correlated statistically to the occurrence of erosions;
- 4) RF IgA presents a clearly distinct behavior in patients who presented or not radiographic erosions, which can have implications in the physiopathogenesis and in the prognostic evaluation of the disease.

Investigations in a larger number of patients with initial RA and longer follow-up are necessary to evaluate the characteristics of RF isotypes titers variations during the disease evolution, its correlation with radiological prognostic, and influence of specific therapeutics.

CONFLICTS OF INTEREST

The author RB works for INOVA Diagnostics Inc., where the serologic tests were performed. RB did not have access to the clinical data of patients previously to the tests results. This study was supported by FINATEC (Santos-Neto LL: 129/2008 – *Universidade de Brasília*). The remaining authors declare no conflicts of interest.

ACKNOWLEDGMENT

We thank Dr. Francisco Aires Corrêa Lima, Dr. Rodrigo Aires Corrêa Lima, Dr. Ana Patrícia de Paula, Professor Cezar Kozak Simaan, Dr. José Antonio Braga da Silva, Dr. Hermes Matos Filho, Dr. Regina Alice von Kircheheim, Dr. Luciana Alves Almeida, Dr. Talita Yokoy Souza, Dr. Jamille Nascimento Carneiro and Dr. Francieli Sousa Rabelo, for forwarding the evaluated patients, and Dr. Paulo Sérgio Mendlovitz, for performing the radiographic tests.

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