Revista Brasileira de Reumatologia

REFERÊNCIA

MUNIZ, Luciana Feitosa et al. Vaccination in patients from Brasília cohort with early rheumatoid arthritis. **Revista Brasileira de Reumatologia**, São Paulo, v. 54, n. 5, p. 349-355, set./out. 2014. DOI: http://dx.doi.org/10.1016/j.rbr.2014.04.002. Disponível em: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0482-50042014000500349&lng=en&nrm=iso&tlng=en. Acesso em: 03 out. 2019.

REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Original article

Vaccination in patients from Brasília cohort with early rheumatoid arthritis

*Luciana Feitosa Muniz**, *Carolina Rocha Silva*, *Thaís Ferreira Costa*, *Licia Maria Henrique da Mota*

Hospital Universitário de Brasília, Universidade de Brasília, Brasília, DF, Brazil

ARTICLE INFO

Article history:
Received 15 June 2012
Accepted 7 April 2014
Available online 21 August 2014

Keywords:
Vaccine
Early rheumatoid arthritis
Brazilian population

ABSTRACT

Introduction: Patients with a diagnosis of rheumatoid arthritis (RA) are at increased risk of infections. Vaccination is a recommended preventive measure. There are no studies evaluating the practice of vaccination in patients with early RA.

Objectives: To evaluate the frequency of vaccination and the orientation (by the doctor) about vaccines among patients with early RA diagnosis.

Methods: Cross-sectional study including patients from the early RA Brasilia cohort. Demographic data, disease activity index (Disease Activity Score 28 – DAS28), functional disability (Health Assessment Questionnaire – HAQ), and data on treatment and vaccination after diagnosis of RA were analyzed.

Results: Sixty-eight patients were evaluated, 94.1% women, mean age 50.7 ± 13.2 years. DAS28 was 3.65 ± 1.64, and HAQ was 0.70. Most patients (63%) had vaccination card. Only five patients (7.3%) were briefed by the doctor about the use of vaccines. Patients were vaccinated for MMR (8.8%), tetanus (44%), yellow fever (44%), hepatitis B (22%), influenza (42%), H1N1 (61.76%), pneumonia (1.4%), meningitis (1.4%), and chickenpox (1.4%). All patients vaccinated with live attenuated virus were undergoing immunosuppressive therapy, and were vaccinated inadvertently, without medical supervision. There was no association between the use of any vaccine and disease activity, functional disability, years of education, lifestyle, and comorbidities.

Conclusion: Patients were infrequently briefed by the physician regarding use of vaccines, with high frequency of inadvertent vaccination with live attenuated component, while immunization with killed virus was below the recommended level.

DOI of original article: http://dx.doi.org/10.1016/j.rbr.2014.04.002.

* *Corresponding author.*
E-mail: luciana_muniz@yahoo.com.br (L.F. Muniz).

http://dx.doi.org/10.1016/j.rbre.2014.04.002

Vacinação em pacientes da Coorte Brasília de artrite reumatoide inicial

Palavras chave:
Vacina
Artrite reumatoide inicial
População brasileira

RESUMO

Introdução: Os pacientes com diagnóstico de artrite reumatoide (AR) apresentam risco aumentado de infecções. A vacinação é uma medida preventiva recomendada. Não há estudos avaliando a prática da vacinação nos pacientes com AR inicial.

Objetivos: Avaliar a frequência de vacinação e a orientação (feita pelo médico) sobre vacinas entre os pacientes com diagnóstico de AR inicial.

Métodos: Estudo transversal incluindo pacientes da coorte Brasília de AR inicial. Foram analisados dados demográficos, índice de atividade da doença (*Disease Activity Score* 28 – DAS28), incapacidade funcional (*Health Assessment Questionnaire* – HAQ), dados sobre tratamento e vacinação após o diagnóstico da AR.

Resultados: Foram avaliados 68 pacientes, sendo 94,1% mulheres, com idade média de 50,7 ± 13,2 anos. O DAS28 foi de 3,65 ± 1,64, e o HAQ de 0,70. A maioria dos pacientes (63%) possuía cartão vacinal. Apenas cinco pacientes (7,3%) foram orientados pelo médico sobre uso das vacinas. Os pacientes foram vacinados para tríplice viral (8,8%), tétano (44%), febre amarela (44%), hepatite B (22%), gripe (42%), influenza H1N1 (61,76%), pneumonia (1,4%), meningite (1,4%) e varicela (1,4%). Todos os pacientes vacinados com vírus vivo atenuado estavam em uso de imunossupressores e receberam as vacinas de forma inadvertida, sem orientação médica. Não houve associação entre o uso de nenhuma vacina e atividade da doença, incapacidade funcional, anos de escolaridade, hábitos de vida, comorbidades.

Conclusão: Os pacientes foram pouco orientados pelo médico com relação ao uso das vacinas, com elevada frequência de vacinação inadvertida com componente vivo atenuado, enquanto a imunização com vírus mortos ficou aquém do recomendado.

Introduction

Infections are an important cause of morbidity and mortality in patients with rheumatoid arthritis (RA).[1] It is estimated that these patients have a two-fold risk of developing infection when compared to healthy subjects of the same sex and age. The increased infectious susceptibility is due not only to the treatment used, but to the disease itself and to associated comorbidities.[2] Infections occur more frequently in joints, bones, skin, soft tissues, and respiratory tract,[2] being responsible, at least in part, for an increase in mortality in patients with RA, especially when they occur in the genitourinary and bronchopulmonary tracts.[3–6]

Vaccination is the primary preventive measure against infectious diseases.[7] In patients with RA, depending on the state of immunosuppression, the immunogenicity of the vaccination may be reduced, but is still effective.[8] There are some cases of RA reported following the use of the vaccine, especially against hepatitis B, but there is no evidence of a causal relationship established. Thus, currently the administration of most vaccines recommended by the national immunization schedule can be performed safely with no effect on disease activity.[7–9]

The use of vaccines not containing living organisms, such as those for influenza (intramuscular), pneumonia, tetanus, diphtheria, pertussis, *Haemophilus influenzae* type B (Hib), hepatitis A and B virus, polio (inactivated – IPV), meningitis and human papilloma virus (HPV), is recommended in patients with rheumatic diseases, including RA.[8,10] Among those, the influenza and pneumococcal vaccines are the most suitable, with a higher level of evidence regarding safety and efficacy. All vaccines should be administered preferably before the start of treatment with synthetic or biological disease-modifying antifheumatic drugs (DMARDs), to try to achieve an adequate immune response.[8,11]

The attenuated live vaccines should be avoided, whenever possible, in patients with rheumatic diseases.[8] Included in this group are the following vaccines: MMR (measles, mumps, and rubella), BCG, influenza (nasal), chickenpox, shingles, typhoid, polio (OPV), smallpox and yellow fever. However, one must make an individualized assessment of patients, considering the degree of immunosuppression and the risk factors for acquiring these infections.[8,12,13]

Despite the recommendations for the use of vaccines in patients with rheumatic diseases, the frequency of vaccination is suboptimal, reaching a maximum of 20%-35% in immunosuppressed patients.[14] However, few studies have evaluated the vaccination coverage of RA patients, with most studies evaluating only influenza or antipneumococcal vaccines.

The only study evaluating vaccination in patients with early RA showed that the response of pneumonia vaccine was lower than that seen in the normal population. Moreover, that study also noted that the addition of infliximab to the therapy with methotrexate did not affect the response to the vaccine.[15]

The Brazilian Society of Rheumatology has recently issued recommendations on vaccination in patients with RA.[16] However, no study evaluating the practice of vaccination, in general, in patients with early RA in Brazil has been published.

Thus, this study aims to evaluate the frequency of vaccination among patients with early RA diagnosis and verify the orientation regarding the use of vaccines given by doctors to patients.

Patients and methods

A cross-sectional study from February 2012 to June 2012, as part of the Brasilia Cohort of Early Rheumatoid Arthritis, was carried out.[17–20] Data collection was performed at the Clinic of Rheumatology, Hospital Universitário de Brasília, Universidade de Brasília (HUB/UnB). We included patients older than 18 years diagnosed with early RA (less than one year of symptoms at diagnosis).

Patients participated voluntarily in the study, after clarification on the content of the research and after signing a free informed consent form. The study was approved by the Ethics Committee of the Faculty of Medicine, Universidade de Brasília (CEP/FM-028/2007).

All participants were assessed by direct interview in routine outpatient consultations. The vaccination card, when available, was checked by evaluating those vaccines used after the diagnosis of RA. If these patients did not possess the vaccination card, they were asked specifically about each and every one of the national immunization schedule recommended vaccines for adults and elderly patients: seasonal influenza, 23-valent pneumococcal – Pn23, MMR, tetanus-diphteria (Td), hepatitis B, and yellow fever.[21] Moreover, they were evaluated with respect to the use of other vaccines: measles, meningococcal, and human papillomavirus (HPV) vaccines. Patients were also asked if they had received some guidance from the accompanying physician on which vaccines they would or would not use.

Information about age, time since diagnosis, disease activity index (Disease Activity Score 28 – DAS28), functional disability questionnaire (Health Assessment Questionnaire – HAQ), use of synthetic or biologic DMARDs (medication, dose), lifestyle (physical activity, current or previous smoking), education, and comorbidities were also obtained through questionnaires and medical record reviews. Patients were then divided into groups, according to whether or not they had received each of the vaccines listed above.

Descriptive statistical analysis was used to evaluate the general characteristics of the study population. The Student's *t*-test or Mann-Whitney test was used to analyze continuous variables. Categorical variables were analyzed by chi-squared or Fisher's exact test, when appropriate. The significance level of 5% ($p < 0.05$) was used for all statistical tests.

Results

Sixty-eight patients with early RA were evaluated. The general characteristics of the patients are shown in Table 1. Regarding the treatment with immunosuppressive drugs, 55 (80%) patients were taking methotrexate, 18 (26%) antimalarial drugs, 17 (25%) leflunomide, 8 (11%) sulfasalazine, 13 (19%) prednisone, 6 (8.8%) infliximab, 1 (1.4%) etanercept, 2 (2.9%) adalimumab, 4 (5.8%) rituximab, and 2 (2.9%) abatacept.

Table 1 – General characteristics of patients diagnosed with early RA evaluated for vaccination.

Characteristics	N (%) or mean ± standard deviation (n = 68)
Women	64 (94.1%)
Age (years)	50.7 ± 13.2
Time since diagnosis (years)	6 ± 2.8
Schooling (years)	8.2 ± 3
Treatment	
Synthetic DMARDs	67 (98.5%)
Biological DMARDs	14 (20.5%)
DAS 28	3.65 ± 1.64
HAQ	0.70 ± 0.6
Vaccination Card	48 (63%)

Of the total group, only five patients (7.3%) had been briefed by the doctor about the use of vaccines. Patients who underwent vaccination without receiving specific medical recommendation made it on their own, inadvertently, at the suggestion of the media or of third parties (relatives/neighbours/acquaintances).

After the RA diagnosis, the use of some kind of inactivated or recombinant vaccine was observed in 57 (84%) patients; and the use of kind of live attenuated vaccine was observed in 32 (47%) patients. The vaccination was carried out as follows: 6 (8.8%) for MMR (measles, rubella, and chicken pox), 30 (44%) for dT, 30 (44%) for yellow fever, 15 (22%) for hepatitis B, 29 (42%) for influenza, 42 (61.7%) for H1N1, 4 (5.8%) for pneumonia, 1 (1.4%) for meningitis, and 1 (1.4%) for varicella (1.4%).

Table 2 shows the analysis of the characteristics of the group that received seasonal influenza vaccine compared to the group of patients who did not receive this vaccine. The same analysis was done for all vaccines under study.

No association among the use of any vaccine and disease activity, functional disability, physical activity, smoking, and years of schooling was noted. Similarly, no difference in frequency of comorbid conditions that could influence the indication of the use of some vaccines, such as cancer and diabetes mellitus, was observed. No patient had chronic lung disease or ischemic heart disease. The guidance on which vaccine patients should or should not use did not result in higher or lower frequency of using any vaccine. Also in patients vaccinated against H1N1 influenza, there was no observed difference in relation to drug therapy or use of other vaccines.

With regard to age, patients who received hepatitis B and MMR vaccines were younger (44 ± 12 *versus* 53 ± 13, $p = 0.03$ and 37 ± 9.5 *versus* 52 ± 13; $p = 0.01$, respectively). The time to diagnosis of RA was longer in the group that received Td (6.8 ± 2.7 *versus* 5.4 ± 2.7, $p = 0.03$) and in those who used H1N1 influenza vaccine ($6{,}7 \pm 2.6$ *versus* 5 ± 2.9, $p = 0.01$). The group that received antipneumococcal vaccine presented higher rate of patients above 60 years (75% *versus* 22%, $p = 0.04$).

Patients using double adult-type vaccine also made more frequent use of MMR (20% *versus* 0%, $p < 0.005$), hepatitis B (47% *versus* 26%, $p < 0.001$) and yellow fever (63% *versus* 29%, $p = 0.01$) vaccines, compared to the group that has not been vaccinated with Td.

No patient receiving hepatitis B vaccine was treated with leflunomide, with a statistically significant difference when compared with patients who did not receive such a vaccine

Table 2 – Analysis of patients according to influenza vaccination.

	Influenza vaccine (n = 29)	Non-vaccinated (n = 39)	p-value
Age	57.9 ± 12.8	45.4 ± 10.8	<0.001
>60 years-old	15	2	<0.001
Time to diagnosis	6.7 ± 2.8	5.5 ± 2.7	0.07
DAS 28	3.6 ± 1.7	3.6 ± 1.6	0.8
HAQ	0.77 ± 0.69	0.60 ± 0.68	0.3
Vaccine guidance	2	3	1.0
Vaccines			
Pneumococcal	4	0	0.029
MMR	3	3	0.6
Yellow Fever	15	15	0.4
Tetanus-diphteria (Td)	20	10	<0.001
H1N1	18	24	0.8
Meningococcal	1	0	0.4
Varicella	1	0	0.4
Prednisone	9	4	0.5
Synthetic DMARDs	28	39	0.4
Methotrexate	25	30	0.5
Leflunomide	7	10	0.8
Antimalarials	7	11	0.9
Sulfasalazine	4	4	0.7
Biological DMARDs	4	10	0.3
Infliximab	1	4	0.3
Adalimumab	1	1	1.0
Etanercept	1	0	1.0
Rituximab	2	2	1.0
Abatacept	0	2	0.5
Smoking			
Current	5	1	0.07
Prior	8	11	0.8
Physical activity	11	21	0.2
Neoplasia	0	1	1.0
Diabetes mellitus	4	1	0.1

(0% *versus* 32%, p = 0.015). Patients vaccinated against hepatitis B also used more frequently MMR (33% *versus* 19%, p = 0.01).

All patients vaccinated with live attenuated viruses (MMR, varicella and yellow fever) were on immunosuppressive therapy. In all these cases, the vaccination occurred without guidance given by Rheumatology Department physicians.

Discussion

Despite the increased infectious susceptibility of RA patients and the importance of vaccination, the practice of passive immunization has been performed improperly in these patients.[10,14] Our study showed that Brasilia cohort patients received little guidance (7.3%) from the physician as to whether or not to use vaccines in general, or specifically in relation to contraindications of live virus vaccines. Thus, most of vaccinated patients in our early RA service received the vaccine on their own, regardless of medical advice. This finding is very important, because the Brasilia cohort is followed-up at an outpatient rheumatology tertiary care service, where the recommendations for vaccination in immunosuppressed patients should be observed.

The lack of recommendation by professionals from a tertiary care service makes us wonder about the situation in relation to the recommendation to be vaccinated in other primary and secondary care centers in our country, and emphasizes the importance of greater disclosure and attention for that matter.

Work done in other countries showed higher frequency of medical guidance as to vaccination, with proportions ranging from 45% to 95%.[22–25] We observed no influence of guidance on the use of any vaccine. However, Doe *et al.* showed improvement in the rate of influenza vaccination after guidance optimization from health professionals, an increase of 56% to 72% in four years of observation.[22,23]

Besides medical guidance, other factors influence vaccination coverage, for instance, vaccination offered at the hospital, allergy to vaccine components, and previous adverse reactions.[22–27] The length of rheumatologists' professional practice may also interfere with the frequency of passive immunization. Desai *et al.* showed a higher proportion of patients vaccinated against pneumonia in the group of rheumatologists with ≤ 10 years of practice.[28] However, a Brazilian study evaluating vaccination practice by pediatric rheumatologists in the state of São Paulo showed no

influence of time of professional practice.[29] In the early arthritis outpatient service where this study was conducted, all rheumatologists have ≤10 years of practice.

We found that the use of some vaccines, such as influenza, tetanus, and hepatitis B, was an important factor for using other vaccines. This may have happened thanks to the best advice given to these patients about the importance of vaccination in general. Furthermore, in the place of application of a particular vaccine (as occurs in primary health services) other vaccines may have been provided, in accordance with age and risk of acquiring other infections.

Regarding vaccination against influenza, we showed that vaccination coverage (42%) was suboptimal, similar to that reported in other studies for RA.[14,22,23] In Brazil, these patients are the target of the National Campaign for Elderly Vaccination, which occurs annually. The goal of the campaign is to vaccinate 80% of the target population against influenza, and, in 2011, it has achieved 84% vaccination coverage.[30] The vaccination for pneumonia was still less frequent (5.8%), and all patients were also vaccinated for influenza. These values are lower than those reported in the literature, ranging from 20.2% to 43%.[25,28] Age over 60 years was a factor that influenced vaccination against influenza and pneumonia, as also was observed in other countries,[24,28,31] which is possibly explained by the extensive media coverage of the National Campaign for Elderly Vaccination.

The vaccine against H1N1 influenza was the most used by our patients (61.7%), thanks to a national campaign due to the pandemic in 2009, which included immunosuppressed patients. This demonstrates that when patients are better targeted, the vaccination coverage can be more effective. In a Brazilian study of RA patients, the vaccine was well tolerated and safe, despite a lower seroconversion.[32]

Infections in patients with RA have gained greater concern with the emergence of the so-called biological agents, including inhibitors of tumor necrosis factor-alpha (anti-TNFα), rituximab, tocilizumab, and abatacept. These drugs are commonly used in combination with traditional DMARDs, further increasing the immunosuppressive effect of these drugs.[10] The use of rituximab may compromise the response of some immunizations, such as pneumococcal and flu vaccines, due to its mechanism of action; thus, the administration of these vaccines is recommended before beginning that medication.[8,33]

Feutchtenbeger *et al.* noted a higher rate of vaccination against influenza and *Streptococcus pneumoniae* in patients who were on anti-TNF or rituximab.[25] However, no difference was observed in relation to medical advice or not vaccination in patients who were using biologicals. In patients vaccinated against hepatitis B, leflunomide was less used – an apparently fortuitous finding. We did not observe an increased presence of liver disease in these patients.

Patients vaccinated for viral hepatitis B and MMR were younger. This is because the target population for MMR vaccine are women 20-49 years and men 20-39 years. Likewise, the national immunization schedule recommends hepatitis B vaccination for adults belonging to risk groups such as pregnant women, health professionals, workers of different areas, and risky sexual groups. This population is also often quoted as being younger.[21]

The low frequency of use of varicella and antimeningococcal vaccines is justified by the non-routine offer of these vaccines by the public health system in Brazil. There was no registry of use of HPV vaccine, which is also currently offered by private medical services.

Vaccination with live attenuated components (MMR, varicella and yellow fever) was very frequent and inadvertently made. The use of live attenuated vaccines should be avoided when possible, but these products may be generally used in moderately immunosuppressed patients, with each case being individually evaluated.[8]

With respect to anti-yellow fever vaccine, Mota *et al.* observed in another study conducted in our department 52 patients with RA who had received this vaccine. Of these, 12.8% had only mild adverse effects. There were no serious reactions or deaths.[12] Considering that yellow fever is endemic in a great part of Brazil, the vaccination against this disease is indicated for the resident population in an extensive part of the national territory (in addition to travellers to these regions). However, the current recommendation is that patients undergoing immunosuppressive therapy should not be vaccinated against this disease.[13]

The study showed that a high percentage of patients in our early RA cohort, living in an endemic area for yellow fever, are vaccinated regardless of medical advice.

It is essential for rheumatologists from endemic areas being able to instruct the patients about areas with recommendation of the vaccine, epidemics and outbreaks, as well as evaluating the individual risk of infection and degree of immunosuppression for each patient.

Although this is the first study evaluating the vaccination status of patients with early RA, it has some limitations. The study did not evaluate the vaccination card of all patients, because the card had been lost by a few individuals. In these cases, the record of the vaccines may not have been done reliably, due to the patients' memory bias. The reasons by which some patients missed out immunization were also not evaluated – such as allergies and previous vaccine reactions, even when they were briefed by the doctor. The knowledge of these reasons would help us to optimize the patients' vaccination coverage. Another limitation was that we did not assess seroconversion, seroprotection and adverse reactions from vaccines.

After this study, our service is trying to offer guidance on the appropriate use of vaccines, and routinely assess the immunization status of patients with early RA. This has been done in form of a checklist, especially prior to treatment with DMDs. Ideally, this assessment should be made not only by rheumatologists in secondary/tertiary care health services, but also at the primary level of health care, by non-specialist doctors and nurses.

In conclusion, patients in our Brasilia cohort of early RA were infrequently briefed by their doctors regarding the use of vaccines; in our view, this can reflect the reality of most services in Brazil. There was a high frequency of inadvertent vaccination with live attenuated virus, with all the risks associated with this practice. The vaccination coverage with killed virus, especially influenza and pneumonia (which are the most recommended) ones, was suboptimal; such vaccination was not the result of the orientation of the

rheumatologist, but to the patient's spontaneous demand for the vaccine.

Thus, both doctors and patients should be better informed as to the necessity of vaccination, given that infections are an important cause of morbidity and mortality in patients with RA. In this scenario, the dissemination and implementation of the recommendations contained in the Brazilian Society of Rheumatology Consensus 2012 on Vaccination in Patients with Rheumatoid Arthritis may be of great importance for improving the clinical practice of rheumatologists.[16]

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgement

Our special thanks to the resident colleagues who helped us in data collection: Meliane Cardoso and Gabriela Jardim.

REFERENCES

1. Michaud K, Wolfe F. Comorbities in rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2007;21:885–906.
2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Artrhritis Rheum. 2002;46:2287–93.
3. Mutru O, Laakso M, Isomaki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. BMJ. 1985;290:1797–9.
4. Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. Br J Rheumatol. 1984;23:92–9.
5. Myllykangas-Luosujarvi R, Aho K, Kautiainen H, Isomaki H. Shortening of life span and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. Clin Exp Rheumatol. 1995;13:149–53.
6. Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25-year prospective study of 100 patients. Ann Rheum Dis. 1990;49:363–9.
7. Conti F, Rezai Soheila, Valesini G. Vaccination and autoimmune rheumatic diseases. Autoimmunity Reviews. 2008;8:124–8.
8. Van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2012;70:414–22.
9. Feuchtenberger M, Voll RE, Kneitz C. Vaccinations in Rheumatology. Z Rheumatol. 2010;69:803–12.
10. Gluck T, Ladner-Muller U. Vaccination in Patients with Chronic Rheumatic or Autoimmune Diseases. Clin Infect Dis. 2008;46:1459–65.
11. Assen SV, Bijl M. Immunization of patient with autoimmune inflammatory rheumatic diseases (the EULAR recommendations). Lupus. 2012;21:162–7.
12. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. Rev Soc Bras Med Trop. 2009;42:23–7.
13. Oliveira ACV, Mota LMH, Santos-Neto LL, Tauil PL. What a Rheumatologist needs to know about yellow fever vaccine. Braz J Rheumatol. 2013;53:206–10.
14. Gluck T. Vaccinate your immunocompromised patients! Rheumatology. 2006;45:9–10.
15. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol. 2007;34:952–7.
16. Brenol CV, Mota LMH, Cruz BA, Pereira IA, Fronza LSR, Bertolo MB, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia sobre vacinação em pacientes com artrite reumatóide. Rev Bras Reumatol. 2013;53:13–23.
17. Mota LMH, Santos Neto LL, Pereira IA, Burlingame R, Ménard HA, Laurindo IM. Autoantibodies in early rheumatoid arthritis: Brasília cohort: results of a three-year serial analysis. Rev Bras Reumatol. 2011;51:564–71.
18. Mota LMH, dos Santos Neto LL, Burlingame R, Ménard HA, Laurindo IM. Laboratory characteristics of a cohort of patients with early rheumatoid arthritis. Rev Bras Reumatol. 2010;50:375–88.
19. Mota LMH, Laurindo IM, dos Santos Neto LL. Prospective evaluation of the quality of life in a cohort of patients with early rheumatoid arthritis. Rev Bras Reumatol. 2010;50:249–61.
20. Mota LMH, Laurindo IM, dos Santos Neto LL. Demographic and clinical characteristics of a cohort of patients with early rheumatoid arthritis. Rev Bras Reumatol. 2010;50: 235–48.
21. Ministério da Saúde. Secretaria de Vigilância em Saúde. In: Departamento de Vigilância Epidemiológica. Manual dos centros de referência para imunobiológicos especiais. 3. ed Brasília: Ministério da Saúde; 2006.
22. Bridges MJ, Coady D, Kelly CA, Hamilton J, Heycock CR. Factors influencing uptake of influenza vaccination in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62:685.
23. Doe S, Pathare S, Kelly CA, Heycock CR, Binding J, Hamilton J. Uptake of influenza vaccination in patients on immunosuppressant agents for rheumatological diseases: a follow-up audit of the influence of secondary care. Rheumatology. 2007;46:716–7.
24. Sowden E, Mitchell WS. An Audit of influenza and pneumococcal vaccination in rheumatology outpatients. BMC Musculoskeletal Disorders. 2007;8:58–62.
25. Feuchtenberger M, Kleinert S, Schwab S, Roll P, Scharbatke EC, Ostemeier E. Vaccination survey in patients with rheumatoid arthritis: a cross sectional study. Rheumatol Int. 2012;32:1533–9.
26. Pradeep J, Watts R, Clunie G. Audit on the uptake of influenza and pneumococcal vaccination in patients with rheumatoid arthritis. Ann Rheum Dis. 2007;66:837–8.
27. Fomin I, Caspi D, Levy D, Varsan ON, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis. 2006;65:191–4.
28. Desai SP, Turchin A, Szent-Gyorgyi LE, Weinblatt M, Coblyn J, Solomon DH, et al. Routinely measuring and reporting pneumococcal vaccination among immunosupressed rheumatology outpatients: the first step in improving quality. Rheumatology. 2011;50:366–72.
29. Silva CA, Terreri MT, Aikawa NE, Carvalho JF, Pileggi GC, Ferriani VP. Prática de vacinação em crianças com doenças reumáticas. Rev Bras Reumatol. 2010;50:3513–61.
30. Ministério da Saúde. Secretaria de Vigilância em Saúde, Programa Nacional de Imunizações. Informe Técnico: Campanha Nacional de Vacinação contra a Influenza. Brasília. 2012.
31. Fahy WA, Farnworth E, Yeldrem KP, Melling GS, Grennan DM. Pneumococcal and influenza vaccination in patients with rheumatic conditions and receiving DMARD therapy. Rheumatology. 2006;45:912–3.

32. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis. 2001;70:2144–7.

33. Bingham CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum. 2010;62: 64–74.