

Special article

Recommendations for the management of influenza A (H1N1) in rheumatic patients with immunosuppression

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ABSTRACT

The Spanish Society of Rheumatology (SER), through a multidiscipline task force, has elaborated a document with specific recommendations for specialists in Rheumatology, emphasizing the special needs of patients with rheumatic diseases, with the objective of informing and orienting health professionals about the current influenza A/H1N1 virus pandemic. All of the recommendations are based on prior documents elaborated by the Ministry of Health and Social Policy task forces, as well as those from the autonomous communities, which are themselves based on the guidelines and documents routinely published by the Centers for Disease Control (CDC) in the US, this being the center designated by WHO for the coordination of efforts against the pandemic. All rheumatologists and potential users of these recommendations are encouraged to consult the original documents, as well as the general guidelines established at each health center.

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Recomendaciones de manejo de la gripe A (H1N1) en pacientes reumáticos con inmunosupresión

RESUMEN

La Sociedad Española de Reumatología (SER), a través de una comisión multidisciplinar, ha elaborado un documento con recomendaciones específicas para los profesionales de Reumatología, atendiendo a las características propias de estos pacientes, con el objetivo de informar y orientar a los profesionales ante la situación actual de pandemia por gripe A/H1N1. Todas las recomendaciones están basadas en documentos previos elaborados por grupos de trabajo del Ministerio de Sanidad y Política Social y de comunidades autónomas, los cuales a su vez se basan en las guías y documentos que elaboran periódicamente el Center for Disease Control (CDC) de EE. UU., como centro designado por la Organización Mundial de la Salud para la coordinación de la pandemia. Se insta a todos los reumatólogos y potenciales usuarios de estas recomendaciones a que consulten los documentos originales, así como las directrices generales que se establezcan en cada centro sanitario.

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Introduction

Many of the patients seen in rheumatology can be included in groups at risk for complications stemming from influenza due to several motives: 1) patients with inflammatory autoimmune processes, the disease itself carries a greater risk of infections; 2) treatment with steroids, disease modifying anti-rheumatic drugs (DMARD), immunosuppressants or biologic agents can increase the risk of serious infection or alter the prognosis of mild infections in the general population; 3) patients with rheumatic disease frequently have visceral (renal, cardiac, lung, endocrine or neurologic) or skeletal (back ankylosis, immobilization) affection that may complicate the course of concomitant infections; 4) patients with rheumatic disease present, in some cases, comorbidity that may suppose an additional risk in the case of pneumonia or other complications such as bronchiectasia, atherosclerosis, ischemic heart disease or osteoporosis with compressive vertebral fracture and respiratory restriction, and 5) some rheumatic diseases are more prevalent in older patients, in whom it is more frequent to find other illnesses coexisting that by themselves constitute risk factors, such as diabetes mellitus, heart failure, renal failure, chronic bronchitis or cancer. In addition, prior experience with the diffusion of recommendations on the part of the Spanish Society of Rheumatology (SER) for prophylactic interventions in immunosuppressed rheumatic patients has shown to minimize the impact of the target infectious disease in an efficient manner.

The SER, through a multidisciplinary commission, has elaborated a first draft document with specific recommendations for rheumatology professionals, attending these patients' special characteristics, with the objective of informing and orienting health professionals faced with the current influenza A (H1N1) pandemic.

All of the recommendations are based on previous documents elaborated by the task force of the Health and Social Policy Ministry (MSyPS) and the autonomous communities, which in turn are based on guidelines and documents periodically elaborated by the Center

for Disease Control (CDC) of the United States, as a center designated by WHO for coordinating efforts against the pandemic (Figures 1 and 2). In addition, because of the pandemics rapid epidemiological behavior, it is expected that the useful life of these recommendations is limited. Therefore, all rheumatologists and potential users of the recommendations are urged to consult original documents as well as general guidelines established by each health center.

Methods

A panel was formed in an urgent manner, by experts designated by SER according to their availability (minimum *quorum*), along with experts in infectious and digestive diseases, who regularly treat patients with intestinal inflammatory disease, for a first reunion. The methodology employed was that of a nominal group. Panel members were asked, before the reunion, to elaborate a list of the aspects to be included in the document or to express an opinion in writing on some concrete aspects. In addition, prior support documentation was provided.^{1,2} Then, results were discussed in the group. The discussion had no major disagreement and the basis of the document was established by unanimity. Discussions at the reunion were organized using Mind Manager Pro® in front of the participants and the resulting document was edited and distributed to the panelists for their comments. A systematic review was not considered for three reasons: the need to act quickly, the excessive novelty of the subjects and experts' experience.

Results

Recommendation targets' objective and risk groups

These recommendations are mainly focused of orienting rheumatologists on the management of patients who are at risk

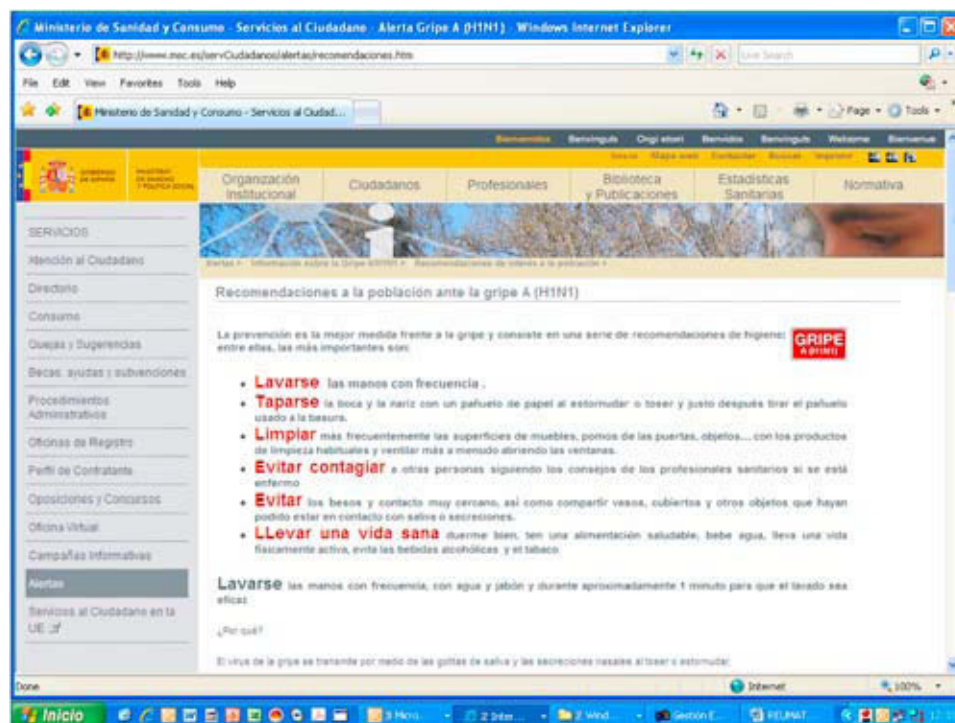


Figure 1. All patients, with or without immunosuppression, have to follow the recommendations currently set by the Health and Social Policy Ministry for all citizens (<http://www.msc.es/servCiudadanos/alertas/recomendaciones.htm>).



Figure 2. Because of the varying nature of the information on the pandemic, all health professionals are encouraged to consult official sources on a regular basis (http://www.cdc.gov/h1n1flu/general_info.htm).

of severe complications due to influenza. These are: 1) patients of any age with systemic autoimmune diseases, among which rheumatoid arthritis, systemic lupus erythematosus, vasculitis or psoriatic arthritis stand out; 2) patients with other rheumatic diseases and the added risk factor of being older than 65 years of age, being younger than 19 and receiving treatment with aspirin, especially patients under 5, pregnant women, obese persons, patients with chronic obstructive pulmonary disease and asthma (especially if receiving steroids for the past year), cardiovascular disease—except isolated hypertension—, active neoplastic disease, chronic renal failure, chronic liver disease, diabetes mellitus, hemoglobin abnormalities (drepanocytosis), transplanted patients or patients with important visceral reactions or wasting, and 3) patients who, independently of disease use the following treatments at any dose: oral, inhaled parenteral or intestinal topical steroids; immunosuppressants: methotrexate, azathioprine, cyclosporin, cyclophosphamide, mercaptopurine, tacrolimus, mycophenolate or leflunomide, or biologics: infliximab, etanercept, adalimumab, tocilizumab, rituximab, abatacept, golimumab or anakinra.

Diagnosis of Influenza A

Diagnostic suspicion of influenza A during the pandemic period, in any person, is characterized by: fever (temperature over 37.8 °C) plus one of the following symptoms: coughing, sneezing, rhinorrhea, sore throat, headaches and myalgia. In the previously established risk groups, during the pandemic and in addition, influenza A may be suspected in the absence of fever, if the patient has at least two other symptoms, or in a patient with pneumonia.

After symptoms appear, the patient must come into contact with community health services following the recommendations of their autonomous communities (primary care physician, telephone 112 or phone numbers established by each community).

The currently accepted diagnostic procedure is H1N1-specific PCR from a naso-pharyngeal exudate. The naso-pharyngeal exudate should preferentially be performed using a round and long swab with no cotton or alginate. It is very important to insert the swab deeply.³

In the immense majority of cases, influenza A has symptoms that are very similar to the common cold; therefore it is difficult if not downright impossible to distinguish the processes by symptoms only. On the other hand, and from what we know until now, influenza A is not behaving more severely than the common cold and progresses satisfactorily with the common measures taken for common colds. In consequence, every patient with cold symptoms must consult his or her primary care physician.

However, all patients with rheumatic diseases including risk groups with fever lasting more than 48 hours, must consult their rheumatologist using channels at their disposal.

Clinical evaluation of these patients must include: 1) chest x-ray, because the risk of pneumonia is larger at 48-72 h; 2) vital signs (temperature, blood pressure, heart rate, respiratory rate); 3) evaluation of baseline blood oxygen through pulse oxymetry; 4) conscience level, and 5) symptoms that indicate infection of low respiratory tract and cardio-respiratory auscultation.

Criteria for hospitalization should be based in the patients' clinical situation. However, pneumonia must be considered as a complication in all cases.

In the case of out-patient follow up, it is recommended that patients with influenza be followed by their primary care physician 48-72 h after their initial consultation.

Prevention

General measures can be divided in two: those for patients at risk and those for health professionals treating them.

General recommendations recommended by the panel are those from the MSyPS, including hand-washing, frequent cleaning, caution when coughing, disposable tissues and avoiding large groups of people.⁴ The MSyPS recommends that patients with cold must remain at home for 7 days after symptom onset (10 for children) or up to 24 h after symptoms abate if their duration is over 7 days.

With regard to rheumatic disease patients at risk, avoidance of exposure to influenza patients, as well as the proper isolation of the latter must be implemented. In case of exposure, the appearance of symptoms compatible with influenza A must be looked for, with daily control of temperature. In the absence of suspicious signs, suspension of any treatment for the rheumatic disease is not recommended. Chemoprophylaxis must be always indicated by a physician and only in the above-mentioned cases.

Health personnel must follow the general recommendations of the MSyPS on avoidance hygiene, protection and self-isolation, if procedent.⁵ It is important that professionals who work in referral centers that tend to influenza A patients be vaccinated against seasonal strains and, in time, against the influenza A (H1N1) strain if so indicated by the ministry. Currently, chemoprophylaxis or antiviral treatment is not indicated except in health personnel with risk factors for complications stemming from influenza. Samples for virology testing should not be taken except in cases where there is a clear indication, according to the diagnostic and therapeutic protocol.

Vaccines

Vaccines against influenza A are still in development. Because their efficacy, safety and availability are still unknown, no recommendations can be established on who to administer them to. In any case, it is to be assumed that, along with other immunocompromised persons, patients reviewed here would be considered as a priority by the ministry. The panel can only recommend being up to date regarding ministry recommendations.

In addition, the panel wishes to emphasize the following, with regard to an eventual vaccine:

- Response of patients undergoing therapy with methotrexate or rituximab may be diminished, because the pneumococcal and influenza virus responses are, but this represents no contraindication for vaccination against influenza A (H1N1) when available.
- Moment of vaccination must be individually assessed. If treatment with rituximab or abatacept is contemplated and the vaccine is available, it is preferable to postpone biologic treatment. However, delaying it may lead to an increase in other immunosuppressants, including steroids. As for timing after vaccination, none can be recommended, although it may be that 4 weeks is enough.
- Vaccination against germs that may complicate influenza A can be clearly recommended, including seasonal flu (yearly) and pneumococcal (every 5 years) vaccines.

It is unknown if vaccination against influenza A will protect patients with rheumatic disease. Extrapolating what we know on vaccination against seasonal flu gives no motives to suspect that there will be differences regarding the results. In fact, the plan against influenza A is a strict protocol designed against seasonal flu.

WHO has established a vigilance network which establishes recommendations on a yearly basis for the composition of the flu vaccine, published in a convenient manner months ahead of starting the vaccination campaign. If no mutations or antigen drift is seen, in other words, there is a good antigenic coincidence between the vaccine and the seasonal epidemic, efficacy of the vaccine ranges from 70 to 90% in healthy adults. Among the non-institutionalized

elderly, hospitalization rates due to the flu are reduced and the appearance of pneumonia in more than 50% and the risk of death are reduced by two thirds.⁶

Vaccination against seasonal flu in rheumatic patients, considered as immunocompromised because of their illness or its treatment, has shown to be effective,⁷ especially in patients with rheumatoid arthritis,⁸ with a good rate of response 6 weeks after vaccination,⁹ although somewhat lower than in healthy persons (response rate of about 70%). Other studies show that it may also be effective in inactive Wegener's granulomatosis,¹⁰ but less effective in patients with systemic lupus erythematosus.¹¹ The vaccine against seasonal flu has been shown to be effective and is not related to reactivation of rheumatoid arthritis.

Treatments may modify antigenic response against the vaccine. There is a larger amount of available information regarding rheumatoid arthritis. Logically, all of the information is related to seasonal flu, but information can be extrapolated reasonably to influenza A vaccination. Before undergoing any potentially immunosuppressive treatment, ideally all necessary vaccinations should be programmed. This is not always feasible and vaccination should not be a motive for delaying treatment.

Steroids. The dose necessary to consider a patient at risk for influenza or other infections is debatable and has no points of agreement. In general, not only for the flu, the relative risk for infections in steroid treated patients varies, according to studies, between a relatively mild relative risk of 1.6 to a higher one of 8.¹² The risk is lower if patients receive less than 10 mg/day of prednisone or its equivalent or if the cumulative dose is under 700 mg. Because of the lack of agreement, it is recommendable to consider patients at risk if receiving any type of dose, especially those receiving more than 10 mg/day of prednisone or its equivalent, or a cumulative dose over 700 mg. With respect to the response to vaccination, there is a study that shown that steroids, independent of their dose and administration, do not alter the response to the vaccine.¹³

DMARD with no immunosuppressive activity. There is no evidence that DMARD with no immunosuppressive activity (hydroxychloroquine, cloroquine or sulphazalazine) have any influence on the appearance of infections, including the flu. Nor is there evidence that they alter the antigenic response of the vaccine against the flu.

Immunosuppressants (including methotrexate). There are few studies showing antigenic efficacy of the flu vaccines in different immunosuppressed groups. In all of them, antigenic response is significant, albeit lesser than in healthy controls. Vaccination is recommended in spite of the fact that response rates can be lower. In one study⁹ the response to the flu vaccine in patients with rheumatoid arthritis was of up to 70%, with a significant difference compared to healthy controls (82%). However, this difference was not related with any treatment and the conclusion was that vaccination was effective in spite of the response being lower. In another study,¹⁴ the antigenic response rate vs. the vaccine in patients with rheumatoid arthritis treated with methotrexate was superior to combinations of DMARD or anti-TNF. Response rates to the vaccine were significant in all groups and vaccination against the flu was recommended, irrespective of treatment. One study analyzed systemic lupus erythematosus (SLE) patients with a mild degree of activity in which therapy with azathioprine was associated with a significantly reduced response vs. other patients with SLE.¹¹ This obliges the clinician to be extra careful in patients with SLE treated with azathioprine in which the vaccine may not be effective.

Biologic therapy. Antigenic response against the flu vaccine in patients receiving combined methotrexate and anti-TNF is less than that developed in patients treated with methotrexate alone, but, as in other cases, the antigenic response is significant and flu vaccine is recommended for patients treated with anti-TNF.^{9,15} One study with rituximab shows that the rate of antigenic response at

4 weeks post-flu vaccination is 18% in patients with rheumatoid arthritis treated with rituximab, a rate significantly lower than patients with rheumatoid arthritis treated with traditional DMARD and that of healthy controls.¹⁶ In spite of the fact that the rate of response is lower in patients with rituximab in this study and, comparatively, the response is lower than that produced with other treatments, it is concluded that patients treated with rituximab should not be excluded from vaccination. In any case, it is preferable to vaccinate before starting rituximab. As for the time that must pass from vaccination until safely starting rituximab treatment, this has yet to be determined.

Influenza A vaccine, as other flu vaccines, will possibly include thymus dependent antigens. The response to this type of antigen is mediated by B-lymphocytes, but requires the activation of T lymphocytes. It is possible that in patients treated with abatacept, the response might be lessened. Abatacept reduces the response both to thymus dependent (tetanus toxoid, flu) and thymus independent (pneumococcal) antigens.¹⁷ Patients treated with infliximab simultaneously receiving methotrexate show a reduced response to the vaccines' antigens, but there is no evidence that the biologic drug reduces the antigenic response even more.

Prophylaxis with antiviral treatment

Not justified at the moment of pandemic, with exceptions. In no case must antiviral drugs be employed systematically as a prophylactic strategy. Elemental prophylaxis is that of the common cold and is published in the MSyPS recommendations. The indiscriminate use of antivirals would lead to resistance to these drugs and, therefore, to a reduced efficiency when administered to patients with serious complications.

Prophylaxis with antivirals could be considered in the case of patients at risk who have been in close and prolonged contact with a confirmed case of influenza A. If prophylaxis is indicated, the earliest start of treatment must be considered. The contagious stage lasts 48 h. Post-exposure prophylaxis should preferentially be administered, in order to avoid future resistance to oseltamivir, inhaled, unless the patient has respiratory disease with the risk of bronchospasm that contraindicate this drug, as follows: 2 inhalations every 24 hours for 10 days, in addition to oseltamivir 75 mg orally every 24h for 10 days.

Treatment

Only patients with a clinical suspicion and risk factor complications or with pneumonia should undergo treatment.

Treatment must preferably start before 40 hours since the onset of symptoms have passed, immediately after obtaining the nasal swab. Treatment consists in oseltamivir 75 mg/12 h for 5 days. 150 mg/12 h for 5 days might be considered if the patient presents diarrhea or is obese or in the ICU. If the nasal swab is negative, treatment must be completed. A negative result does not exclude the infection completely. If the patient has received treatment for 3-4 days, it is better to complete it in order to avoid resistance. Children may present more adverse events with oseltamivir (nausea, vomiting, overall, but also neuropsychiatric manifestations as in adults), and strict surveillance in order to detect these must be instituted.

It is advisable to suspend background immunosuppressive or biologic therapy for 7 to 15 days at the physicians' discretion, except in the case of steroids. Depending on the severity of the patients' disease, an increase in steroids can even be contemplated as in any other situation that places an increased demand on the suprarenal axis.

Discussion

Each physician will have to weigh the risk to the patient in relation to the severity, activity and treatment of the underlying disease. However, as a general message, even though this is a very contagious flu pandemic, it is of a reduced lethality in relation to other epidemics, including seasonal flu; therefore, the panel does not consider it necessary to take any extraordinary precautions in other patients commonly treated by rheumatologists.

Another general consideration is that, even if the pandemic affect young patients not previously exposed to a type A (H1N1) virus pandemic, patients older than 65 are those at a greater risk of developing pneumonia due to the flu. Therefore, in absolute terms, more pneumonia in younger persons is expected, but older patients will have a higher relative risk.

It is important to attain high vaccination rates against seasonal influenza, because the mortality from seasonal viruses is still larger than that from the new virus A (H1N1). In addition, reducing the impact of seasonal flu would allow the relocation of resources vs. the pandemic and the results from an eventual coinfection with the seasonal strain are yet unknown.

The SER, through its web page, will attempt to inform its members of all relevant changes to the current recommendations that are of national interest. These recommendations are also available in an extended format at the SER web page (www.ser.es). Additionally, we have included links to the source documents with real-time updating.

All health professionals, and therefore rheumatologists and allied health personnel, must be constantly informed and have the minimum training in order to transmit confidence and tranquility to patients, avoiding the introduction of unnecessary doubts or veering from the consensus direction of the health authorities or specific consensus expert groups.

Thank you

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