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Review article

What a rheumatologist needs to know about yellow fever vaccine

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ABSTRACT

Patients with rheumatic diseases are more susceptible to infection, due to the underlying disease itself or to its treatment. The rheumatologist should prevent infections in those patients, vaccination being one preventive measure to be adopted. Yellow fever is one of such infectious diseases that can be avoided. The yellow fever vaccine is safe and effective for the general population, but, being an attenuated live virus vaccine, it should be avoided whenever possible in rheumatic patients on immunosuppressive drugs. Considering that yellow fever is endemic in a large area of Brazil, and that vaccination against that disease is indicated for those living in such area or travelling there, rheumatologists need to know that disease, as well as the indications for the yellow fever vaccine and contraindications to it. Our paper was aimed at highlighting the major aspects rheumatologists need to know about the yellow fever vaccine to decide about its indication or contraindication in specific situations.

O que o reumatologista deve saber sobre a vacina contra febre amarela

Palavras-chave:
Febre amarela
Vacina contra febre amarela
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RESUMO

Os pacientes portadores de doenças reumáticas são mais suscetíveis à infecção, quer seja pela própria doença de base ou pelo tratamento empregado. É papel do reumatologista prevenir as infecções nesse grupo de pacientes e, dentre as estratégias empregadas, encontra-se a vacinação. No grupo das doenças infecciosas que podem ser prevenidas está a febre amarela. Sua vacina é segura e eficaz na população em geral, mas, assim como as vacinas contendo organismos vivos atenuados, deve ser evitada sempre que possível em portadores de doenças reumáticas em uso de medicamentos imunossupressores. Sendo a febre amarela endêmica em grande parte do Brasil, e estando a vacinação contra essa doença indicada para a população residente em extensa parte do território nacional (além dos viajantes para essas regiões), torna-se essencial que o reumatologista tenha conhecimento da doença, das indicações e contraindicações da vacina contra a febre amarela. Nosso artigo tem o objetivo de destacar os principais aspectos que o reumatologista precisa conhecer

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sobre a vacina contra a febre amarela, para decidir por sua indicação ou contraindicação após avaliação do risco-benefício em situações específicas.

Introduction

The treatment of rheumatic diseases has improved over the years.[1] The prescription of immunosuppressive drugs, usually early or even aggressive, is aimed at reducing and eventually eliminating disease activity.[2] That immune system manipulation inherent to therapy in association with the autoimmune disease dysfunction can increase the risk for infections in that group of patients.[2,3] The risk for severe infections in that population is two times greater than that in the general population.[1]

Vaccination is one of the most effective measures to prevent infectious diseases.[2,4] However, the vaccination of rheumatic patients on immunosuppressive therapy requires some special considerations. Its efficacy can be jeopardized due to the immune system changes characteristic of those patients.[4] In addition, there is the risk of disease activation following immunization.[4,5]

Vaccines containing attenuated live organisms should be avoided whenever possible in rheumatic patients on immunosuppressive drugs.[2,4] These vaccines represent an increased risk to patients who cannot fight infections; in addition, vaccines can lead to manifestations similar to those of primary disease.[2] The yellow fever vaccine is one of such vaccines.[2,4]

Yellow fever is endemic in a large area of Brazil, the yellow fever vaccine being indicated for the population living in that area and for travelers to that area; therefore, rheumatologists need to know that disease, as well as the indications for the yellow fever vaccine and contraindications to it. Our paper was aimed at highlighting the major aspects rheumatologists need to know about the yellow fever vaccine to decide about its indication or contraindication in specific situations.

Yellow fever

Yellow fever is an infectious, hemorrhagic, febrile, viral disease, which is noncontagious (it is not transmitted through contact) and endemic in regions of the Africa and South America, being caused by a single-stranded RNA virus.[6] In Brazil, since 2009, the Ministry of Health, based on epizootics occurring in 2008 and 2009, divided the regions according to their potential of yellow fever transmission into areas with recommendation for vaccination, previously called endemic and of transition, and areas without recommendation for vaccination, previously called disease-free areas. The areas with recommendation for vaccination are as follows: the North and West-Central Brazilian regions; the states of Maranhão and Minas Gerais; and part of the states of São Paulo, Piauí, Bahia, Paraná, Rio Grande do Sul and Santa Catarina.[7,8] The disease is transmitted by the bite of hematophagous mosquitoes of the *Culicidae* family, especially of the *Aedes* and *Haemagogus* genera.[6] Its transmission comprises two cycles: the urban and the sylvatic.[6] In Brazil, the last urban cases were identified in 1942. Since then, the disease cases reported have been of sylvatic transmission.[6]

Susceptibility to yellow fever is general and neither a race nor an age group more or less susceptible to the virus is known.[6] The most affected individuals are young males, because of greater exposure.[6] The mean incubation period ranges from 3–6 days.[6]

The clinical findings vary from lack of symptoms or short-duration mild fever to a severe and fulminant infection.[6,9] In moderate and severe forms, the following can occur: kidney and liver failures; heart disorders; hemorrhage; and shock.[9] The overall fatality rate ranges from 5%–10%.[6] Only 10% of the cases are estimated to be severe forms, associated with high fatality rate, ranging from 40%–60% of the cases.[6] According to the Ministry of Health, the mean fatality rate is 52.8%, ranging from 23%–100%.[7]

Yellow fever cannot be eradicated because it is a zoonosis.[10] Disease outbreaks occur every 5 to 7 years.[7] There is no specific treatment for the disease.[6] Regarding the general measures to be taken, the fight against the *Aedes aegypiti* mosquito is one of the major aspects to consider in combating the urban form. Appropriate garbage collection and water supply, use of larvicides, health education provided by government institutions, and population awareness to reduce transmission should prevent water stagnation, such as in flowerpots, gutters or untreated swimming pools. Regarding the urban form, wild areas should be avoided in regions with recommendation for vaccination if no immunization was performed in the period from 10 days and 10 years from the trip.[6–8,10] The yellow fever vaccine is the major way to prevent that disease.[6]

Yellow fever vaccine

The yellow fever 17D vaccine has been available in Brazil since 1937.[10,11] Over 500 million doses have been used worldwide.[12] It is considered to be one of the most effective and safe vaccines in the world.[12] It provides protection for at least 10 years, and even lifelong protection.[6,13] Within 30 days from vaccination, more than 90% of the individuals develop antibodies against yellow fever.[9] About 98%–100% of the individuals vaccinated become immunized.[13,14] Nevertheless, the World Health Organization recommends a booster shot every 10 years.[13]

Vaccination should be performed from the age of 9 months in areas with recommendation for vaccination according to the Ministry of Health. In situations of epidemic or outbreak, it should be performed from the age of 6 months.[7]

The original 17D strain has been developed from 176 passages of the wild Asabi strain in murine and gallinaceous tissues.[13] The vaccines currently used derive from two sub-

strains, 17DD and 17D204,[11,13] which are obtained from 287–289 and from 235–240 passages, respectively.[13] The passages are aimed at attenuating the virulence of the virus.[11] In Brazil, the vaccine used is the 17DD, produced in Biomanguinhos, an agency of the Fundação Oswaldo Cruz.[6]

After immunization, low viremia is detected in half of the individuals vaccinated.[13] There is rapid induction of humoral response and immunoglobulin M (IgM) can be detected in 7 to 10 days.[13] Neutralizing antibody titers as low as 1:10 are sufficient to provide protection.[13]

The 17D strain is a potent inducer of CD4+ and CD8+ cytotoxic T responses.[13] The innate immune system is also involved, because the 17D strain replicates minimally in dendritic cells, and can lead to their apoptosis.[13] The toll-like receptors (TLR) 2, 3, 7, 8 and 9 are stimulated and the IFN-α/β/γ, TNF-α and IL-1β levels increase.[13,15]

Adverse effects

Although safe, the 17DD vaccine still has adverse effects, usually well tolerated. The following effects are considered mild and usually occur between 2 and 11 days after vaccination: local pain; inflammation; mild headache; myalgia; back pain; and transient elevation in transaminases.[13,16]

Anaphylaxis secondary to yellow fever vaccine is another relevant effect that occurs at the frequency of 0.9 to 1.8 per 100,000 doses, being attributed to allergy to egg or vaccine-related gelatin allergy.[12,16,17]

The most relevant serious adverse effects (SAEs) are the yellow fever vaccine-associated neurotropic disease (YEL-AND) and the yellow fever vaccine-associated viscerotropic disease (YEL-AVD).[6,13,18] According to data of the Information System of the National Immunization Program of the Brazilian Ministry of Health, 1994 adverse effects were reported from 2000 to 2008, when 101,564,083 doses of the 17DD vaccine were administered.[17] The SAEs occurred more frequently after the administration of the first dose than after revaccination. There were 0.023 cases of anaphylactic shock, 9 cases of hypersensitivity, and 0.84 episodes of YEL-AND for every 1,000,000 doses. Twenty-six cases of viscerotropic disease were identified. During that period, there was an increase in publications on SAEs in Brazil.[17]

Yellow fever vaccine-associated neurotropic disease (YEL-AND)

The incidence of YEL-AND worldwide is estimated to be between 0.4 and 9.9 for every 100,000 doses.[12] It is more frequent under the age of 6 months, whose incidence varies from 0.5 to 4 cases for every 1,000 vaccines.[19] The occurrence of YEL-AND decreased after suspending vaccination to that age group.[20]

YEL-AND might manifest as encephalitis, meningitis, neuropathy, myelitis or Guillain-Barré syndrome.[12,16,19] Its clinical findings are typically mild, with complete recovery.[19]

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)

In 2001, the first cases of YEL-AVD were reported,[18,21,22] although a retrospective analysis indicates its occurrence in the 1970s.[13] In Brazil, the expected frequency is 0.006 to 1.32 cases per 100,000 doses.[13] The risk of YEL-AVD increases with age. The risk for patients aged 60 to 69 years is 4.2 per 100,000 doses, and it might reach 12.6 per 100,000 doses in those over the age of 75 years.[16]

It is a severe condition, whose expected fatality rate is about 60%.[13] On average, the symptoms begin four days after vaccination, the findings being identical to those of the infection by the wild virus.[6,23]

Studies on YEL-AVD are scarce, because of the small number of cases.[13] Most cases reported, except for the outbreak in Ica, Peru, have been related to different vaccine lots.[13,23] Thomas et al.,[24] in a systematic review, have estimated between 11.1 and 15.6 SAEs per million doses administered.

The gene sequencing obtained from individuals with YEL-AVD is identical to that of corresponding vaccine strains.[12,23] This suggests that YEL-AVD is more related to host conditions, who cannot control vaccine replication, than to mutations of the vaccine virus.[12]

Considering those findings, some risk factors for SAEs have already been identified: advanced age (over 60 years); male gender; thymectomy; and use of immunosuppressive drugs.[13]

Yellow fever vaccine and rheumatic patients

Chronic rheumatic patients on immunosuppressive drugs are more often exposed to infection, and, thus, their immunization has been increasingly studied and recommended.[1,4]

However, according to current recommendations, the yellow fever vaccine should be avoided or even contraindicated to that group of patients, because it is an attenuated live virus vaccine with risk for uncontrolled vaccine viral replication.[4,13,25,26] The European League Against Rheumatism (EULAR) recommends that live virus vaccines should be avoided and their risk should be weighed.[4] According to the British Pediatric Rheumatology Group, live virus vaccines are contraindicated to all patients on cytotoxic drugs.[27] However, the Brazilian Immunization Consensus for Children and Adolescents With Rheumatic Diseases recommends that children and adolescents with rheumatic diseases on immunosuppressive agents should not receive live virus vaccines, referring specifically to yellow fever.[26] Da Luz states that the vaccine should not be administered to immunocompromised patients, because of their high risk of encephalitis.[3] Hayes has contraindicated vaccination to those patients and encouraged the creation of new vaccines.[12] However, there is no specific recommendation regarding rheumatic patients at risky areas, temporarily or not, and who are susceptible to the disease. Still regarding rheumatic patients, cases of YEL-AVD have been reported in patients with systemic lupus erythematosus and rheumatic polymyalgia.[17,22,23] Thus, analysis of the risk of infection and possible SAEs associated with vaccine in that population is required.

The immunosuppression degree should be assessed and varies according to the disease, the immunosuppressive drugs used, their dose and use duration.[26] The disease influences the intensity of immunodeficiency because it also defines the dose and duration of treatment.[28] There is no consensus about the minimum dose that causes clinical immunosuppression, and there is little evidence about the immunodeficiency caused by cytotoxic drugs at doses used for rheumatic diseases.[27] Regarding corticosteroids, the use of prednisone at

equivalent doses of 10 mg/day has not been associated with an increase in infection.[28] Prednisone doses at equivalent doses of 2 mg/kg/day for more than one week or 1 mg/kg/day for more than one month are contraindication to live virus vaccines in those patients.[27] The British Pediatric Rheumatology Group admits immunization with live virus in patients with juvenile idiopathic arthritis who are not on immunosuppressive drugs,[27] indicating that immunosuppression can be more related to therapy than to the underlying disease.

Another factor to be considered is the seroconversion capacity of those patients, which is inversely proportional to their immunosuppression degree.[25] Regarding the immune response of rheumatic patients, a study has assessed 17 patients with rheumatoid arthritis on biologics, who received the yellow fever vaccine. Their pre- and post-vaccine IgG and IgM titers were measured by using a method with sensitivity and specificity similar to those of the plaque reduction assay to determine neutralizing antibody titers (gold standard to assess protective immune response). Comparing the antibody titers of patients and controls, a tendency towards a reduced response in the group studied was observed, although a statistical analysis could not be performed because of the small number of patients.[29]

The only study about the adverse effects in that population has assessed 70 patients with several rheumatic diseases, with a mean age of 46 years, who inadvertently received the yellow fever vaccine. Of those patients, 16 (22.5%) reported minor adverse effects, which is in accordance with that expected for the healthy population.[30]

It is worth noting that, in general, vaccines can be related to the development of autoimmune diseases. Viral molecular structures can induce the immune activation of cells of the innate defense system and lead to self-sustained chronic inflammation.[31] The time interval between vaccination and the occurrence of autoimmunity can vary from days to years, making its identification difficult.[5] There have been reports of cases in which the yellow fever vaccine has triggered autoimmune diseases, such as multiple sclerosis, transverse myelitis and Kawasaki disease.[32–34] Cases of autoimmune hepatitis and of multiple evanescent white dot syndrome have been reported in association with hepatitis A vaccination.[35,36] Infections and immunizations can also promote immunomodulation, leading to a reduction in the exacerbated inflammatory activity.[31] Regulatory T cells activated in that process can be investigated in the control of inflammation and autoimmunity.[31] Similarly to that which happens with allergic diseases, the "hygiene hypothesis" suggests that the relative absence of infections would account for the increasing incidence of autoimmune diseases.[31]

Final considerations

The current recommendation is that patients on immunosuppressive drugs should not be vaccinated against yellow fever.[2,4] The vaccine with the inactivated virus is being developed and has shown good protective immune response in murines.[37] However, the occurrence of periodical outbreaks enables the appearance of new cases before the vaccine is available for the population.

So what to do with patients living in endemic areas, close to the wilderness or who are exposed during work?

There are no other studies assessing the response to yellow fever vaccination or its adverse effects in rheumatic patients on immunosuppressive drugs. Due to ethical reasons, that vaccine cannot be administered to those patients for scientific research purposes. In addition, conclusive results can only be yielded after assessing a large number of patients, because adverse effects seem to be rare, even in that population. To assess the cost-benefit ratio, the risk of contracting the infection should be compared with the risk of contracting the disease.[25]

The immunosuppressive dose used is fundamental to support the physician's decision. According to the American Academy of Pediatrics, prednisone at equivalent doses of 2 mg/kg/day or 20 mg/day or greater doses contraindicate vaccination with live virus vaccines (*Varicella Zoster*).[38] The Brazilian Immunization Consensus for Children and Adolescents With Rheumatic Diseases of the Brazilian Society of Rheumatology, when considering the yellow fever vaccine, states that rheumatic patients should not receive live virus vaccines, a type of vaccine that is usually contraindicated in immunosuppressed individuals.[26]

In specific cases, a window of opportunity can exist before starting the immunosuppressive drugs, when the live virus vaccines can be administered.[27] According to the British Society of Rheumatology, vaccination should occur two weeks before beginning the treatment.[27] According to that same group, at least three months should be waited for immunization with those vaccines.[27] Specialists advocate the risk/benefit analysis for patients on corticosteroids and/or cytotoxic drugs. The EULAR specialists state that those vaccines should be avoided, but the risks and benefits should be considered.

It is up to the assistant physician to instruct patients about the areas with recommendation for vaccination, epidemics and outbreaks, as well as to assess the individualized risk of infection and the immunosuppression degree of each patient so that the yellow fever vaccine can be properly indicated.

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Conflicts of interest

The authors declare no conflicts of interest.

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