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BRIEF REPORT

Seroconversion of rheumatoid arthritis patients after yellow fever vaccination

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Abstract

Vaccination is a current strategy used to prevent infections in patients with immune-mediated rheumatic diseases. However, the use of live-attenuated vaccines prepared from living microorganisms in these patients should be avoided due to the risk of acquiring infections. The present study aimed to investigate the effect of the yellow fever (YF) vaccine (a live-attenuated vaccine) in 12 patients with rheumatoid arthritis (RA). The sample comprised 12 patients (9 females and 3 males; mean age 52.2 ± 6.5 years) with RA, who inadvertently received fractionated 17D yellow fever vaccination during an outbreak of this disease. In this cohort, 10 were administered leflunomide; 7 were administered methotrexate; 6 were administered prednisone (median dose of 5.0 mg/day); 6 took biologic drugs; and 1 took tofacitinib. All but one patient (used rituximab, prednisone, and methotrexate) seroconverted. None of them developed clinical signs of infection after the procedure. The fractionated dose of the YF vaccine is effective and safe in the observed sample.

Key Points

- *Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at a high risk of acquiring infections*
- *The fractionated dose of the YF vaccine is effective and safe in the observed sample*
- *Vaccination against YF should be avoided in patients with AIIRD under immunosuppression owing to the risks of inducing YF infection*

Keywords Live-attenuated vaccine · Neutralizing antibodies · Rheumatoid arthritis · Yellow fever

Introduction

Yellow fever (YF) is an acute febrile infectious disease caused by a mosquito-borne virus of the *Flaviviridae* family. The cycle of transmission of the yellow fever virus (YFV) and the illness is more prevalent in densely populated, poor urban settings of tropical and subtropical areas of South America and Africa, causing epizootics and periodic outbreaks [1, 2].

Since 2016, Brazil has experienced one of the worst cases of YF epidemics. Within the last 80 years, Brazil has recorded an exponential increase in the number of cases and YF-associated deaths across the forest, contiguous areas, spanning the country's largest cities in the Southeast and South regions, in which the trend of urbanization significantly increases the risk of the disease [3]. Vaccination is the primary preventive strategy against the virus, and Brazilian authorities have developed the Brazilian National Immunization Program to launch a massive vaccination campaign in response to this outbreak.

Max Theiler and colleagues developed a live-attenuated YF vaccine in 1937, which was one of the safest and most

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successful vaccines ever used globally. Three sub strains (17DD, 17D-204, and 17D-213) are used for the production of the 17D vaccine virus, following the immunogenicity and safety aspects [2, 4]. In Brazil, the YF vaccine is produced by Biomanguinhos-Fiocruz (https://www.bio.fiocruz.br), and 17DD is the main strain used for its production [1].

Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at a high risk of acquiring infections when compared with patients without AIIRD [5, 6]. Thus, vaccination is important in preventing the rate of infectious diseases caused by YFV and the rate of hospitalization of this category of patients [7]. Nevertheless, live-attenuated vaccines should be considered with caution in AIIRD patients, as these vaccines contain live micro-organisms that might cause infections in a susceptible host [8]. According to the 2019 update of the European League Against Rheumatism (EULAR) recommendations for vaccination in adult rheumatic patients, live-attenuated vaccines should be avoided during immunosuppression, with exception of cautious use of herpes zoster and measles booster under special circumstances [8].

YF can cause a wide range of clinical manifestations, from mild-to-severe diseases; it can lead to the rapid evolution of acute liver failure and provoke death [8]. Therefore, the risk–benefit evaluation of YF vaccination in immunocompromised patients is of great concern and almost no data exist that may help the clinical decision in this context.

The present study discusses the seroconversion and neutralization of antibody production against YFV of a rheumatic patient cohort who inadvertently receives YF vaccination during a national immunization campaign. The results contribute to knowledge in this area.

Methods

Twelve patients with rheumatoid arthritis (RA), admitted into the rheumatology center of the Hospital Universitário Evangélico Mackenzie, Southern Brazil, received a single dose of the YF 17DD vaccine (587 IU per dose, considered a fractionated dose). None of them had previously received vaccination against YF. Of this group, 10 patients received leflunomide, 7 received methotrexate, 6 received biologic DMARDs (2 infliximab, 2 tocilizumab, 1 abatacept, 1 rituximab), 6 received prednisone (doses from 2.5 to 10 mg/day; median 5.0 mg/day), and 1 received tofacitinib (for more details, refer to Table 1).

Serum conversion and neutralizing antibody production were measured by Plaque Reduction Neutralization Test (PRNT 50) in cell culture.

Table 1 Data on 12 rheumatoid arthritis patients receiving yellow fever vaccination

Number	Gender	Age (years)	Side effects	Interval between vaccination and blood collection (weeks)	Seroconversion	PRNT	Disease duration (years)	Disease activity (DAS28VHS)	RF	Prednisone (mg/day)	MTX (mg/week)	LFN	Others
1	F	59	0	88	Y	1120	14	7.14	-	5	0	Y	Tocilizumab
2	F	53	0	89	Y	1243	8	2.53	-	0	10	Y	Tocilizumab
3	F	53	0	87	Y	200	8	4.87	+	0	25	Y	Infliximab
4	M	57	0	88	Y	265	16	4.75	+	2.5	0	Y	Infliximab
5	F	60	0	89	U	20	22	5.0	+	10	25	N	Rituximab
6	F	42	0	95	Y	732	8	3.73	-	5	0	Y	Abatacept
7	F	47	0	95	Y	1505	8	1.39	-	0	0	Y	0
8	M	47	0	89	Y	1031	6	2.8	-	10	25	Y	0
9	F	48	0	46	Y	650	5	3.79	-	0	20	N	0
10	F	61	0	212	Y	73	13	2.5	+	0	10	Y	Tofacitinib
11	M	44	1	113	Y	1362	6	1.6	+	0	0	Y	0
12	F	56	0	111	Y	3473	6	5.17	+	5	25	Y	0

PRNT plaque reduction neutralization test, *RF* rheumatoid factor; *MTX* methotrexate; *LFN* leflunomide; *F* female; *M* male; *Y* yes; *U* unknown

Vero E6 cells were maintained in a 5% CO_2 atmosphere at 37 °C, in DMEM/F-12 media with 10% inactivated fetal bovine serum (FBS), and 1% penicillin/streptomycin. The concentration used for PRNT was 1.0×10^5 cells per well, seeded in 24-well plates 24 h before the test. For each sample, serial twofold dilutions starting at 1:10 in DMEM/F-12 media and 1% penicillin/streptomycin were carried out. Afterward, a suspension of the YFV 17DD virus (the concentration required to obtain an average of 70–80 plaques) was dispensed into all wells. In the neutralization step, the mix (virus plus sera) was incubated for 1 h at room temperature. After this period, the mixture was added to 24-well plates seeded with cells and incubated at 37 °C for 1 h. Then, the medium was completely discarded and replaced with an overlay containing 1.6% carboxymethyl cellulose (CMC) and 4% FBS in DMEM/F-12 media with 1% penicillin/streptomycin. Plates were incubated at 37 °C in a 5% CO_2 atmosphere for 7 days. The monolayers were fixed with paraformaldehyde (3%) and stained with crystal violet. Plaques were counted, and the $PRNT_{50}$ titer was calculated.

Yellow fever antibody titers were classified as follows: $PRNT_{50}$ titers ≥ 50 indicated positive serology; $PRNT_{50}$ titers < 5 indicated negative serology; $PRNT_{50}$ titers ≥ 5, and < 50 indicated undetermined serology.

The PRNT 50 test was conducted in the Molecular Virology laboratory at Instituto Carlos Chagas/Fiocruz PR, 46 to 212 weeks (median 89 weeks) after vaccination.

This study was approved by the Research Ethics Committee of the Mackenzie Evangelic School of Medicine with an Approved No. 4.221.307. All patients signed informed consent.

Results

The study presents a description of 12 patients with RA. Despite contraindication, they were vaccinated against YF. Altogether, the patients (3/12 males; 9/12 females with a mean age of 52.2 ± 6.5 years of age) had RA with a median disease duration of 8 years (Table 1). In the sample, 58.3% of patients had disease activity after vaccination, and no post-vaccination difference was recorded. Only one patient had indeterminate seroconversion (PRNT value 50: 20), a 60-year-old patient who received rituximab (4 cycles, last cycle 4 months before vaccination), methotrexate (25 mg/week), and prednisone (10 mg/day) as treatment and who had moderately active RA disease. Since the analyzed sample was collected 89 weeks after vaccination, we could not determine if the patient did not seroconvert nor if there was a decrease in the anti-YFV neutralizing antibody titers over time.

Only one patient reported adverse side effects of vaccination: a 44-year-old male who complained of a limited episode of fever. Four of the observed patients were considered to be with the active disease when immunized (Table 1).

Discussion

The seroconversion and follow-up clinical symptoms of 12 individuals with RA, inadvertently vaccinated with the live-attenuated 17DD YF vaccine demonstrated a robust antibody response, and no serious adverse reactions were observed. One of the patients (number 10, Table 1) using tofacitinib and prednisone (10 mg) at vaccination time was positive 4 years after receiving the inoculation. A 60-year-old female (number 5, Table 1), using rituximab, methotrexate (25 mg/week), and 10 mg of prednisone with the disease of long duration (22 years) and with the disease during the immunization had undetermined results in the PRNT assay. Only one patient (number 11, Table 1) presented a mild reaction of a fever episode after the YFV immunization.

All patients received the fractional dose of the vaccine. This was a strategy used recently to overcome the YF vaccine shortage. Formulations of the lower dose (587 IU) have shown to be equivalent to reference formulation (27,476 IU) of immunogenicity and side effects with the exception of local injection pain, found more frequently with the standard dose (9). Moreover, no significant differences in the viremia levels are noted among the groups, which have been demonstrated by the viral plaque formation or quantitative real-time-PCR (qRT-PCR) (9–11). The fractionated formulation contributed to the good tolerance observed in RA patients is unknown.

According to 2019 EULAR recommendations, vaccination against YF should be avoided in patients with AIIRD under immunosuppression owing to the risks of inducing YF infection. The Brazilian Rheumatology Society recommends YF vaccination for patients living or traveling to YF-endemic areas owing to the seasonal epidemic outbreaks in the country. In these cases, the immunosuppressive oral therapy should be withdrawn > 3 months to immunization. Biological therapy of > 5.5 half-lives and rituximab of 6 months should also be withdrawn before immunization [9].

From a study using 278 AIIRD patients with controlled underlying disease, in which immunosuppressive medications were withdrawn according to previous recommendations, primary vaccination with 17DD-YF was safe. In addition, the immunogenicity of therapeutic proteins in patients with AIIRD was safe [10]. Moreover, booster vaccination was administered to 17 RA patients during

anti-TNF alpha treatment; only one patient was seronegative, and none of them reported symptoms connected to the YF vaccine administration [11]. Another study demonstrated the effects of YF vaccination on 31 AIIRD patients. Of these patients treated with biologic therapy (3 using infliximab and 3 using rituximab) [12] and inadvertently re-vaccinated for YF, 87.1% became seropositive and only 4 patients had mild side effects (arthralgias, myalgias and fever, and rhinorrhea). In the present series, we did not measure antibodies before immunization. However, all patients stated not having previous immunization or the disease. Thus, we believed this was their first contact with the YF virus.

Our study examined the immunological status and post-vaccination effects in a small sample of patients, and all patients received the fractionated dose of the YF vaccine. This study can expand the knowledge of the seroconversion status in patients with autoimmune RA diseases. The study may guide the decision in situations where the benefits outweigh the risks and where the YF vaccine is to be administered with caution.

Declarations

Ethics approval This study was approved by the Committee of Ethics in Research 4.221.307 from Mackenzie Evangelic School of Medicine, PR, Brazil.

Disclosures None.

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