Yellow fever vaccination in Brazil: Short-term safety and immunogenicity in juvenile autoimmune rheumatic diseases

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ABSTRACT

Yellow fever vaccine (YFV) is a live attenuated vaccine usually contraindicated for juvenile autoimmune rheumatic disease (JARD) patients. During the recent epidemic in Sao Paulo-Brazil, YFV was indicated for patients under low immunosuppression. Thirty JARD patients with inactive diseases undergoing low immunosuppression and 30 healthy controls (HC) were vaccinated with a fractional dose 17DD YFV (~5495 IU) and evaluated 30 days later. JARD patients and controls had comparable median age (12.4 vs. 12 years, p = 0.250). Disease parameters remained stable 30 days after 17DD YFV (p > 0.05) and only mild adverse events were reported in both groups (p > 0.05). JARD and HC had similar seroprotection [93% vs. 100%;p = 0.49], seroconversion rates [96% vs. 100%;p = 0.489], and GMT [1249 vs.1293; p = 0.821]. Both groups had similar white-blood-cells kinetics with transient decreases in lymphocytes at D5 and neutrophils at D10, followed by full recovery at D30 (P < 0.05). In conclusion, 17DD YFV was safe and immunogenic in JARD. This study may contribute to recommendations for patients living/-travelling to endemic areas.

Introduction

Children and adolescents with juvenile autoimmune rheumatic diseases (JARD) are more susceptible to infections. In this context, vaccination is an effective measure to reduce associated morbidity and mortality. Non-live vaccines studies reported adequate safety and immunogenicity profiles for these patients [1–4].

Yellow fever vaccine (YFV) is a live attenuated immunization not routinely recommended for JARD patients. Nevertheless, according to Pan American Health Organization (PAHO) and World Health Organization (WHO) recommendations, during the recent vaccination campaign in the state of Sao Paulo, this live attenuated vaccine was indicated with a fractional dose for patients under low immunosuppression [5].

There are, however, no data regarding fractional YFV safety for JARD patients. Therefore, the aim of this study was to evaluate the short-term safety of immunization with fractional YFV in JARD patients.

Methods

This is a prospective controlled and open study conducted in the context of the yellow fever outbreak between February and May 2018 comprised 30 consecutive JARD patients and 30 healthy controls with ages > 2 to ≤ 18 years old, living in high risk areas for yellow fever. All JARD patients had inactive diseases and received low dose immunosuppression: prednisone (≤0.5 mg/Kg/day or 20 mg/day), sulfasalazine, hydroxychloroquine, methotrexate (≤0.4 mg/Kg/week or 15 mg/week) or leflunomide (20 mg/day), following EULAR recommendations for JARD patients [6]. Patients under other immunosuppressive drugs were not included.

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Nádia Emi Aikawa, V. Andrade Balbi, Eduardo Ferreira Borba et al.

Vaccine: X 10 (2022) 100131

Patients were regularly followed at the Pediatric Rheumatology Unit of Children's Hospital, University of Sao Paulo, and fulfilled the international classification criteria for juvenile idiopathic arthritis (JIA) [7], juvenile systemic lupus erythematosus (JSLE) [8], juvenile systemic sclerosis (JSS) [9], juvenile dermatomyositis (JDM) [10] and Henoch-Schönlein purpura (HSP)/IgA vasculitis [11]. Of these 30 JARD patients, 16 patients had JIA, 6 HSP, 4 JSLE, 3 JDM and 1 JSS.

Exclusion criteria included pregnancy or breastfeeding, previous YFV, anaphylactic response to vaccine components or to egg, previous vaccination with any live vaccine four weeks before or any inactivated vaccine two weeks before the study, acute infection resulting in fever over 37.8 °C up to three days prior to vaccination, blood transfusion within three months, primary immunodeficiency diagnosis, asplenia and individuals whose legal representatives disagreed to participate in the study.

A single subcutaneous (arm) fractional dose [one fifth (0.1 mL) of the standard dose] of the 17DD YFV, produced by Biomanguinhos/FioCruz(Brazil), lots 174uVFA034Z and 178VFC089Z, was administered to all participants. The fractional dose of 0.1 mL corresponds to $\sim$ 5495 IU and it is above the minimum potency recommended by WHO (>1000 IU). Patients and controls were evaluated on the day of vaccination (D0) and four weeks later (D30). Demographic data of all participants were collected at first visit. Current concomitant treatment of patients was assessed on D0 and D30. Disease activity was evaluated according to specific tools for each JARD on D0 and D30: juvenile arthritis disease activity score 71 (JADAS71) for JIA patients [12], Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) for JSLE [13], childhood myositis assessment scale (CMAS), disease activity score (DAS) and manual muscle testing (MMT) for JDM [14].

Blood samples were obtained from JARD patients and controls immediately before vaccination (D0) and after five days (D5), 10 days (D10) and 30 days (D30) for laboratory parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count, C-reactive protein (CRP), serum urea and creatinine]. Leukopenia was defined as leukocyte count <4000/mm^3, lymphopenia as lymphocyte count <1500/mm^3 and neutropenia as neutrophil count <1500/mm^3. Erythrocyte sedimentation rate (ESR) was assessed in JARD patients on D0 and D30.

Safety assessment. A rigorous follow-up of adverse events was performed during the first 30 days after vaccination. On the day of vaccination, a diary card containing a list of possible adverse events was given to parents and included local reactions (pain, redness, swelling and itching) and systemic adverse events (arthralgia, fever, headache, malaise, fatigue, myalgia, diarrhea, nausea/vomiting, abdominal pain, cutaneous rash, dizziness, tremor, bleeding, bruises). Participants were asked to give "yes/no" responses for each event and to bring their diary cards at each visit. Other adverse events that were not on the list should also be reported. Participants could contact investigators at any time by phone call if necessary. Serious adverse events were defined as those resulting in hospitalization or death.

Immunogenicity assessment. All JARD patients and healthy controls were evaluated on the day of vaccination and 30 days later. Serology against YF virus (PV010/18YFV) was performed by Plaque Reduction Neutralization Test (PRNT) at the Laboratory of Viral Technology at Fundação Oswaldo Cruz. The immune response to YFV vaccination was evaluated by Plaque Reduction Neutralization Test (PRNT) at baseline and D30. Seroprotection (SP) was defined as PRNT $\geq$ 3.15 log10 mIU/mL (1:100) and seroconversion (SC) as negative SP at baseline and positive SP at D30. Geometric mean titers (GMTs) of YF-antibodies were also calculated [15].

This study was approved by the local institutional Ethical review board, and informed consent was obtained from all participants. The study was registered with clinicaltrials.gov under NCT03430388.

Statistical analysis

Categorical variables were presented as number (percentage) and continuous variables as mean ± standard deviation or median (range). Comparisons between JARD and controls were performed using Fisher's exact test analyzing by 2x2 contingency table for categorical variables and two-sided Student's *t*-test or Mann-Whitney *U* test for continuous variables. Prospective analysis of continuous variables was performed by One Way Repeated Measures Analysis of Variance (ANOVA) and Friedman Repeated Measures Analysis of Variance on Ranks, followed by Tukey Test to determine where the difference occurred between the time points. The adopted significance level in all analysis was set at 5%.

Results

JARD patients and healthy controls had comparable median age [12.4 (6.3–18.2) vs. 12 (6.9–18.7) years, p = 0.250]. The frequency of female gender was significantly higher in JARD patients compared to controls [21/30 (70%) vs. 10/30 (33%), p = 0.009], whereas Caucasian race was similar in both groups [15/30 (50%) vs. 15/30 (50%), p = 1.000].

Vaccine safety. Disease activity parameters of JARD patients remained unchanged from D0 to D30: JADAS71 [6.5 (1–22) vs. 6 (1–31), p = 0.744], SLEDAI-2 K [1 (0–2) vs. 0 (0–2), p = 1.000], CMAS [52 (52) vs. 52 (52), p = 1.000], DAS [0 (0–1) vs. 0 (0), p = 0.500] and MMT [80 (80) vs. 80 (80), p = 1.000]. Erythrocyte sedimentation rates [6 (1–27) vs. 5.5 (1–31) mm/1st hour, p = 0.874] and CRP levels [0.3 (0–4.16) vs. 0.3 (0.3–3.4) mg/dL, p = 0.489] remained stable 30 days after YFV. HSP and JSS patients persisted stable throughout the study.

Nine JARD patients and 15 controls (30% vs. 50%, p = 0.187) had no adverse effects. Both studied groups had only mild symptoms during follow-up, with similar frequencies of local and systemic adverse events (p > 0.05). The most frequent reactions similar in both groups were headache (33.3% vs. 13.3%, p = 0.125), myalgia (13.3% vs. 6.7%, p = 0.671), malaise (10% vs. 0%, p = 0.237), nausea (10% vs. 3.3%, p = 0.237) and diarrhea (6.7% vs. 10%, p = 1.000). None of JARD patients and healthy controls had severe adverse events.

YF vaccine immunogenicity. Complete YF serology (D0 and D30) was available in 24 JARD patients and 25 controls. At baseline, seroprotective antibody titer $\geq$ 1:100 was seen in 1/24 (4%) of patients with JARD and 1/25 (4%) of controls (p = 1.000). After 30 days, vaccine seroprotection rate was comparable in JARD patients and controls [93% vs 100%; p = 0.49], as well as seroconversion rate [96% vs. 100%; p = 0.489]. GMT after immunization [1249 (95% CI 964–1617) vs. 1293 (95% CI 1128–1482); p = 0.821] were also similar in JARD and control group.

Both groups had similar median white-blood-cells count kinetics with transient decreases in leukocyte and neutrophil levels on D10 (p < 0.05), followed by full recovery to baseline levels on D30. For lymphocytes the decrease occurred at D5 with complete recovery in D30 (p < 0.05). Of note, frequencies of leukopenia (<4000/mm^3), neutropenia (<1500/mm^3) and lymphopenia (<1500/mm^3) remained low and stable with rare new onset cases after YFV (Table 1). Only one JARD (25%) and 2 healthy controls (40%) with neutrophils < 1500/mm^3 at D10 were neutropenic at baseline. None of JARD patients and healthy controls had increased of AST, ALT, serum urea and creatinine levels throughout the study.

Table 1

Prospective analysis of white blood cells in juvenile autoimmune rheumatic diseases (JARD) patients and healthy controls (HC) after yellow fever vaccination.

JARD (n = 30)	D0	D5	D10	D30	P
Leukocytes, cells/mm³	6100 (4080–9390)	5370 (3300–8240)	5250 (3400–10920)	6340 (3850–9670)	0.002 [abe]
Leukopenia, < 4000/mm³, n (%)	0 (0)	3 (10)	4 (15)	1 (4)	>0.05
Neutrophils, cells/mm³	2900 (1390–4870)	2680 (1250–4990)	2420 (1260–6960)	3260 (1580–5710)	0.007 [be]
Neutropenia, < 1500/mm³, n (%)	1 (3)	3 (10)	3 (10)	0 (0)	>0.05
Lymphocytes, cells/mm³	2040 (1220–5350)	1680 (650–3940)	1980 (1090–3140)	2110 (1180–6000)	<0.001 [ad]
Lymphopenia, < 1,500/mm³, n (%)	3 (10)	8 (27)	3 (10)	3 (10)	>0.05
HC (n = 30)					
Leukocytes, cells/mm³	6560 (3790–11050)	6465 (3380–10940)	5130 (2590–11180)	6825 (3180–9540)	<0.001 [bce]
Leukopenia < 4000/mm³, n (%)	2 (7)	2 (7)	7 (23)	2 (7)	>0.05
Neutrophils, cells/mm³	3115 (1110–6740)	3095 (980–6090)	2260 (470–4440)	3240 (640–6680)	<0.001 [bce]
Neutropenia < 1500/mm³, n (%)	3 (10)	2 (7)	5 (17)	2 (7)	>0.05
Lymphocytes, cells/mm³	2555 (1620–4210)	2040 (1060–7110)	2000 (1140–6370)	2295 (1330–3940)	<0.001 [abd]
Lymphopenia, < 1500/mm³, n (%)	0 (0)	5 (17)	2 (7)	1 (3)	>0.05

Results were presented as median (range) or n (%).

D0- vaccination day, D5 − 5 days after vaccination, D10 − 10 days after vaccination, D30 − 30 days after vaccination.

[a] Comparison between D0 and D5 medians with p < 0.05.

[b] Comparison between D0 and D10 medians with p < 0.05.

[c] Comparison between D5 and D10 medians with p < 0.05.

[d] Comparison between D5 and D30 medians with p < 0.05.

[e] Comparison between D10 and D30 medians with p < 0.05.

Discussion

To our knowledge this was the first prospective study demonstrating that fractional dose of 17DD YFV was safe and well tolerated in JARD patients. We further demonstrated that this vaccine does not trigger disease flares.

The advantage of the present study was the prospective design since the only three previous reports in adult patients with rheumatic disease that were retrospective, precluding a definitive conclusion about the YFV safety [16–18]. In addition, the use of a standard protocol with consecutive clinical and laboratorial evaluations allowed a more accurate identification of possible adverse events. The rheumatic disease group was homogeneous with regard to low immunosuppression and inactive disease activity in spite of the diverse and limited representation of each disease. A limit of our study is the small sample size, which precludes evaluating not frequent adverse events.

More than two thirds of our JARD patients reported mild signs and symptoms after primary YFV, particularly headache, myalgia and diarrhea. In contrast, only 22.5% of adults with rheumatic diseases under immunosuppression that were inadvertently revaccinated with full-dose of YFV reported minor adverse events, mainly myalgia [16–18].

Similarly, safety studies of other live vaccines in JARD patients (such as measles, mumps and rubella (MMR), and varicella-zoster) demonstrated no severe side effect in JIA, JSLE, JDM and JSS patients [1,19–21]. In recent studies with children and adolescents with autoimmune rheumatic diseases, live-attenuated MMR booster vaccines were safe and did not induce disease flare, even in patients under immunosuppressive and biologic therapies [19,21]. On the other hand, a case series (n = 17) of rheumatic patients with autoimmune and autoinflammatory conditions, and under anti-IL-1 or anti-IL-6 therapy, serious adverse events were reported in 12% of patients and disease flare in 41% [22], suggesting the need for larger prospective trials in order to acquire more robust evidence on live attenuated vaccines in this population.

Regarding vaccine immunogenicity, we identified an overall good response against fractional YFV in JARD patients, that exhibited 96% of seroconversion, similar to previously demonstrated in the pediatric healthy population (98%) after fractional dose [23]. Moreover, the GMT values after immunization were above 1000 in JARD herein, reaching the levels of healthy children in previous study [23]. This finding reinforces that low dose immunosuppression did not impair vaccine response besides a good safety profile in this population. Of note, a recent randomized, controlled trial demonstrated 10 years protection after fractional-dose of yellow fever vaccine and suggested that there is no need for a booster vaccination [24,25]. However, persistence of this vaccine induced immunogenicity in JARD under immunosuppression has not been assessed yet.

Neutrophils and lymphocytes were assessed, as a safety surveillance measure after YF vaccine, especially considering the potential of cytopenia associated with autoimmune rheumatic disease itself and the immunosuppressive therapy. We provide novel evidence that YFV has a mild and transient deleterious effect in white-blood-cells count. The kinetics is similar in JARD patients and health controls with an initial decrease in lymphocytes followed by a decrease in leukocytes and neutrophils, and a subsequent full recovery of these cells in one month. Interestingly, absolute neutropenia, mostly grade 2 (1000 to 1499/mm³), has been reported after immunization with live vaccines, mostly in the first 2 weeks after vaccination and with resolution 21 days later. Possible factors associated with neutropenia included low baseline neutrophil counts prior to vaccination and black ethnicity [26], which was not confirmed by our data. The mechanism underlying this alteration is unknown but a complex modulation of innate immune response including natural killer (NK) cells, neutrophils and monocytes elicited by 17DD YFV resulting in elevated levels of plasma interferon (IFN) 15 days after vaccination has been demonstrated [27]. In this context, the possible role of the latter in cell kinetics deserves further studies, since IFN-I signaling may cause altered inflammatory response or immune suppression during viral infections [28].

Disease safety was observed herein with stable JARD and acute-phase reactants parameters throughout the YFV study contrasting with disease aggravation observed in 4% JIA patients after measles, mumps and rubella vaccination [18]. Self-limited varicella-rash also occurred in 18% of JIA patients receiving methotrexate and corticosteroid after varicella-zoster vaccination [19].

In conclusion, fractional dose of 17DD YFV seems to be safe in JARD patients under low immunosuppression, reinforcing its recommendation in pediatric patients living or travelling to endemic areas. The non-requirement of a booster dose in these patients requires further studies but it is supported by the reassuring findings of long-term protection in the general population with the fractional dose regimen.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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