Safety and Immunogenicity of the Quadrivalent Human Papillomavirus Vaccine in Patients with Juvenile Dermatomyositis: A Real-World Multicentre Study

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Abstract

**Background:** Concerns about the safety and efficacy of vaccinations in patients with pediatric rheumatic diseases, such as juvenile dermatomyositis, have led to contradictions and low vaccination coverage in this group, who are at a higher risk of infections, including by human papillomavirus (HPV). Although HPV vaccine should be recommended for all juvenile dermatomyositis patients, there is a lack of data to support the safety of this vaccine. The aim of this study was to assess the safety and immunogenicity of the quadrivalent HPV vaccination in juvenile dermatomyositis patients.

**Methods:** Juvenile dermatomyositis patients aged from 9-20 years and healthy controls were enrolled to receive a 3-dose schedule of quadrivalent HPV vaccination from March/2014 until March/2016. Study visits were performed before the first dose, one month after the second and third doses and one year after the first dose. Participants completed a diary of possible adverse events following each dose, and disease activity was measured. At each visit, serum samples was collected for testing antibody concentrations. Participants recruitment was conducted in ten Brazilian centers. From 48 eligible patients, 42 completed the 3 doses schedule of the vaccine (5 patients had received doses previously). The McNemar test and the Kappa concordance coefficient were applied to compare the disease activity scores used for juvenile dermatomyositis patients between quadrivalent HPV vaccine doses and before the vaccination. The software used was SAS 9.4.

**Results:** No severe adverse events were related to the vaccination. The disease activity scores were usually low, and remained stable, or even improved during the follow-up. After three vaccine doses the juvenile dermatomyositis group presented seropositivity of 100% for HPV16 and 97% for HPV18, similarly to the control group who presented 100% for both. One year after the first dose the seropositivity for the patients group was 94%
Conclusions: The HPV vaccination in juvenile dermatomyositis patients is safe and immunogenic. Since the seropositivity against HPV16 and HPV18 was very high after the 3-dose schedule, this regimen should be recommended for juvenile dermatomyositis patients.

Background

There are some concerns regarding the safety and efficacy of vaccines related to autoimmune diseases (AID) and their immunosuppressive treatments (1, 2). The uncertainties surrounding this issue may impact directly on the vaccination of patients with pediatric and juvenile rheumatic diseases, leading to a low vaccination coverage in these special groups of patients. Numerous studies have shown that patients with AID are at a higher risk of infections and their complications, such as the human papillomavirus infection (HPV). In fact, a metanalysis have shown that women with systemic lupus erythematosus have a four times higher risk of oncogenic HPV compared to healthy women (3, 4). Adult and pediatric dermatomyositis patients are also more prone to complications and mortality from serious and opportunistic cutaneous and systemic infections (5).

HPV vaccine is a powerful weapon to avoid the infection caused by the main HPV subtypes. Notably, HPV 6 and 11 subtypes are responsible for the development of 90% of condylomata acuminata and the 16 and 18 subtypes for approximately 70% of cases of cervical cancer, 90% of anal cancer, 60% of vaginal cancer, and 50% of vulvar cancer worldwide (6).

Although the quadrivalent HPV vaccine (qHPV) has been widely used by the healthy population since its launch in 2007, there is still a lack of studies in patients with AID to support its recommendation, especially among the pediatric population (7).

The qHPV has been implemented in Brazilian National Immunization Programs (NIP) to
adolescent girls since 2014 (8) in a 3-dose schedule (0 and 6 months, and 5 years). Currently the vaccination schedule comprises two doses (0 and 6 months) for healthy children and adolescents (9) and it was extended to girls from nine to fourteen years old and boys from eleven to fourteen years old, as well as to immunocompromised from nine to twenty-six years old including the 3-dose schedule (10).

The aim of this study was to evaluate the safety and immunogenicity of the qHPV vaccine in a multicentre Brazilian prospective study involving juvenile dermatomyositis (JDM) patients.

Methods

This was a multicentre prospective controlled observational cohort study adapted from the Dutch protocol used from the study of safety and immunogenicity of the bivalent HPV vaccine in children with Juvenile idiopathic arthritis (68 patients), childhood systemic lupus erythematosus (6 patients) and JDM (6 patients) with a real-world approach (11, 12).

In the present study a 3-dose schedule (0, 1 or 2, and 6 months) of the qHPV vaccine (against HPV6, HPV11, HPV16, HPV18) was used in patients who met the Bohan and Peter’s criteria for JDM (13), from 9 to 20 years old, and age-matched healthy controls (HC). The doses of the qHPV vaccine used in the study were received by donation from the local Special Immunobiological Reference Centers of NIP.

Participants who were eligible and willing to receive the qHPV vaccine were enrolled in the study from March 2014 until March 2016. Moreover, JDM patients who had already received one or two doses of the qHPV vaccine before inclusion were also allowed to participate, as a care standard to reach three doses, which is indicated for immunosuppressed patients (14), since this is a real-life study.

Patients were recruited in 10 pediatric rheumatology units from tertiary centres of different Brazilian regions. Patients were selected regardless of medication used to
constitute a real-life setting. HCs were recruited from patient peer groups in two study sites. The protocol under the code U1111-1211-2150, was approved by all the local ethics committees and informed consent was obtained from each participant and their guardians. Study visits were planned before the first dose, one month after the second and third doses, and one year after the starting dose.

**Main Outcome Measures**

For safety evaluation of the qHPV vaccine, participants were asked to complete a diary for 14 days after each dose, about the occurrence of possible local and/or systemic adverse events following vaccination (AEFV). The local AEFV addressed included redness, bruising, edema, induration, and pain. Systemic AEFV included fever, skin abnormalities, itchiness, headache, nausea, vomiting, fatigue, fainting, and muscular and articular pain. Another outcome considered for safety evaluation in JDM patients included the assessment of disease activity at each study visit, using muscular and cutaneous parameters. For muscular evaluation the Childhood Myositis Activity Score (CMAS) and Manual Muscle Testing (MMT) were used. The CMAS ranges from 0 (high disease activity) to 52 (no disease activity) (15), and the MMT ranges from 0 (high disease activity) to 80 (no disease activity) (16). To verify whether disease activity had changed post vaccination, the CMAS and MMT values were compared between visits, considering as stable disease when the scores changed less than 20%; worsening if the scores decreased at least 20%; and improvement when both scores increased at least 20%. The most usual cutaneous manifestations of JDM, cutaneous rash, heliotrope of the upper eyelids and Gottron papules, were evaluated in each visit according to their intensity by the same Pediatric rheumatologist and compared as follow: improvement, if the manifestation has subsided; stable, if it remained unchanged; worsening, if it had aggravated.
Comparison of the medications in use at each visit, which can indirectly quantity disease activity intensity, was used as an additional parameter, as follows: stable disease, if the medication remained the same between the visits; improvement if it had been withdrawn and worsening if a new treatment had been added or if previous treatment doses were increased.

In order to compare the changes in the measured values, considering CMAS and MMT scores, cutaneous manifestations, and use of medications, according to the established criteria already specified, three comparisons were made: Comparison 1: after two doses versus baseline; Comparison 2: after three doses versus baseline; and Comparison 3: after three doses versus after two doses.

As good practice in clinical trials, all participants received the investigators’ contact details and were guided to contact the hospital if any symptom occurred during the study period, or in case of any doubt regarding the study protocol. Each participant centre had the autonomy to decide whether their patients would continue to receive the qHPV vaccination in case of disease worsening.

For immunogenicity evaluation, blood drawing was performed at each study visit. Serum was collected and frozen under -70ºC in Brazil and subsequently shipped to the Netherlands for serologic antibody concentration testing using a virus-like particle based multiplex Luminex assay (12). Seropositivity for HPV16 and HPV18 was defined as an antibody concentration higher than 9 Luminex Units/ml and 13 Luminex Units/ml, respectively.

Data were organized in the Microsoft Excel program v16.23 according to participant group (JDM or HC), and whether the participant completed the protocol or not. Descriptive analyses were performed for the qualitative variables. Data were presented in numbers (percentages) for categorical variables and in median (range) for continuous variables.
Graphs and tables were prepared in Affinity Designer 1.6.1 and GraphPad Prism v7. The statistical significance of the categorical data was tested with the Fisher’s exact test, using IBM SPSS statistics v21. P values less than 0.05 were considered as significant. In addition, the McNemar test (17) and the Kappa concordance coefficient (18, 19) were applied to compare the disease activity parameters scores used for JDM patients between pos the qHPV doses and before the vaccination. The hypothesis tested was the vaccination no induce flare or worsening of disease activity. The software used for the analyses was SAS 9.4 (20).

The null hypothesis was considered for these tests when the frequency of variables considered to evaluated disease activity were the same in the period pre and post vaccination.

Results

Forty-seven JDM patients and 41 HC were initially eligible for the study. Four JDM patients and two participants from the HC group had previously received one dose of the vaccine. One patient had received two doses. During study period, five patients did not finish the study protocol of 3 doses-schedule: three of them due to lose the follow-up, one patient with active disease fearing AEFV, and the last one became pregnant after receiving two doses. Forty-two JDM patients and 35 HC individuals completed the 3-dose schedule. The number of participants included in the study is presented in figure 1. Baseline characteristics of the participants are summarized in table 1. Median age at diagnosis of JDM was 7.7 years. Median age at first dose of qHPV vaccine was similar between JDM patients and HC (13.5 vs. 15.6 years. Seventy-five percent of the JDM patients used at least one medication for disease control at baseline. Hydroxychloroquine was the most commonly prescribed medication, used by 20/47 (42.6%) of the patients. Corticosteroids were used by 40.4% of the patients, with a median dose of 10 mg/day.
Only 3/47 (6.4%) patients were using Cyclophosphamide at baseline.

Concerning AEFV evaluation, a total of 121 diaries (40 after the first dose, 41 after the second dose, and 40 after the third dose) from 47 JDM patients were analyzed, as well as 111 diaries (38 after the first and second doses and 35 after the third dose) from 41 HC individuals. The occurrence of AEFV is described in table 2. Pain was the most common local adverse event reported for both JDM patients (62.5%) and HC (60.5%) after the first dose. After the third dose, despite the decrease in frequency, local pain remained the most common local symptom reported by 40% of the JDM group and 54.3% of the HC.

Headache was the most frequently reported systemic adverse event after the first and second HPV doses among patients and controls. Muscular and joint pain were more prevalent after all doses in the patients group in comparison to the HC group. The frequency of the other systemic symptoms was less than 5% for patients and controls. No differences were observed in the comparative frequency analyzes between JDM patients and HC and no severe adverse events were related to the vaccination.

In total, JDM patients had 44 baseline visits, 44 visits after the second dose, 40 visits after the third dose, and 27 visits one year after the starting dose. These results are described in figure 1.

The median of disease activity measured through the CMAS score was 50 at the first visit, 51.5 at the second visit, and 50 at the third and fourth visits. Regarding the MMT score, the median was 79 at the first and second visits and 80 at the third and fourth visits. The scores remained stable in the majority of patients after receiving the second and third qHPV doses compared to baseline (comparisons 1 and 2, respectively). None patient presented worsening in the scores in these comparisons, and five patients (10.6 %) even demonstrated improvement in comparison 2 (CMAS scores increased 15 to 20 points in these five patients). The analyses of disease activity performed six months after the end
of the 3-dose schedule showed that three patients presented worsening scores in comparison with the scores presented immediately after receiving the third dose. Two of these three patients returned to the score that they had at baseline. Only one patient remained with a final score lower than her baseline score. The changes in CMAS and cutaneous manifestations are shown in figure 2.

Thirty-four percent of patients presented at least one typical cutaneous manifestation at baseline (19.1% cutaneous rash, 25.5% Gottron papules, and 14.9% heliotrope of the upper eyelids). Regarding the patients that already presented a skin abnormality at baseline, improvement in the lesion occurred in five patients with a rash (55.5%), two with Gottron papules (16.6%), and three with heliotrope (37.5%). Worsening or new lesion occurred in one patient with a rash (11.1%) and two with heliotrope (25%) during comparison 2. The complete analysis of skin activity can be seen in figure 2.

None statistical difference was presented by McNemar test considering rash and heliotrope (p-values > 0.05). Moreover, the Kappa coefficient analyses have allow us to confirm that qHPV vaccine haven’t influence in disease activity of JDM vaccinated patients (p-values >0; <1). The complete analyzes by these 2 tests are shown in table 3.

The medication used by each patient was also evaluated. Throughout the study, the majority of patients maintained the same (stable) treatment. Only three JDM patients initiated a new medication during the study period: one methotrexate, another azathioprine, and the third mycophenolate. However, these three patients already presented active disease before receiving the initial qHPV dose.

It is important to note that the patient who started using methotrexate had it suspended after the third dose because of improvement in the disease activity. In addition, the three patients who were taking cyclophosphamide during the study (table 1), evolved with regression of disease activity and stopped taking this immunosuppressive drug.
Baseline blood samples were collected from 37 JDM patients and 39 HC individuals. At baseline, 5% of HC were seropositive for HPV16 and 3% for HPV18. Seropositivity at baseline for JDM patients was 27% for HPV16, and 24% for HPV18. Five patients and two HC individuals had been vaccinated before the study, and therefore a baseline sample was not taken. Of the 13 patients who were seropositive for HPV 16 and/or HPV18 at baseline, only two reported being sexually active at the time of the study and therefore they were excluded from the serological analyses (figure 1).

Thirty-six JDM patients received the first two doses of qHPV vaccine and had a blood sample collected after the doses. After the second dose, the seropositivity was 94% and 92% for HPV16 and HPV18, respectively. Seropositivity of the 31 JDM patients who completed the 3-dose schedule was 100% for HPV16 and 97% for HPV18. Only one JDM patient remained seronegative for HPV18 immediately after receiving all three doses. This patient was under a low dose of oral glucocorticoid associated with hydroxychloroquine and azathioprine.

Blood samples were available for 17 JDM patients one year after the first dose (six months after the final dose). This analysis showed that 94% remained seropositive for HPV16 and HPV18. Only one patient became seronegative for both HPV types. This patient was using only cyclosporine during the study period. The 3 JDM patients that were using cyclophosphamide during the vaccination had demonstrated seropositivity for both HPV serotypes. The HC group have responded to the vaccination after two and three doses, with 100% seropositivity for both HPV serotypes (samples available from 14 HC after two doses, and from 31 after three doses). The serological analysis is shown in figure 3.

Discussion

This is the largest prospective study addressing safety and immunogenicity of a qHPV in a
pediatric population with JDM. This study is in real life setting, where patients were included despite their disease activity and the use of glucocorticoids and/or immunosuppressive treatment, since this is a 3-dose schedule vaccination during a 6 months period, precluding the possibility of drug withdrawal, unless they were on remission.

Even so, the qHPV vaccine was safe and immunogenic in this cohort of patients. Besides no severe adverse events were related to the vaccination, the occurrence of AEFV in the two weeks following vaccination was similar between JDM patients and the HC group. All AEFV were mild, such as local pain, headache, muscular and articular pain, or fatigue, and presented spontaneous resolution shortly after the vaccination and we could observe a decrease in the occurrence of the majority of AEFV throughout the study among both, patient and HC groups.

Moreover, disease activity particularly muscular and cutaneous manifestations, were low overall and remained stable or even considerably improved during the study period.

Our results support a currently published metanalyses’ study on the influence of HPV in AID, where no association was identified for bivalent and qHPV vaccines (1). Importantly, the ultimate data just published on the occurrence of AEFV after 3 years of using qHPV vaccine in the Brazilian NIP for girls, that are in accordance with those from other countries and corroborate the safety of HPV vaccines (21).

The seropositivity of JDM patients for HPV16 and HPV18 after the 3-dose schedule was high (almost 100%), even among patients who were using immunosuppressive therapy. This result was surprisingly good, as it is generally accepted that patients using immunosuppressive drugs, especially at high doses, present a diminished response to vaccinations (22, 23, 24).

A limitation of our study is that some patients and HC individuals did not complete the
study protocol. This reflects the real-world practice, where patient care is strongly impacted by the social-economic problems of the country and the study population (25). Daily challenges have to be surpassed in developing countries such as Brazil, such as the clinics and hospitals are in general remote outreach, thus the patients need traveling to the follow-up visits, what lead to missed them and difficult compliance to the treatment. Our study reflects this routine clinical practice. The high seropositivity rates at baseline may suggest that some patients and controls did not report sexual activity. Our results are in accordance with other studies addressing HPV vaccinations in patients with AID (26, 27, 28). In those studies, HPV-vaccination induced seroconversion in the large majority of patients. In addition, we have showed that one year after the first qHPV dose the majority of patients who received the 3-dose schedule remained seropositive for HPV16 and HPV18. HPV vaccination was shown to have a safe profile and adequate immunogenicity in JDM patients. The 3-dose regimen reached very high seropositivity for HPV16 and HPV18 without inducing any flare-ups regarding disease activity or any severe AEFV. Therefore, this schedule should be recommended in this population with a high risk of developing oncogenic HPV. Long-term follow-up studies are still necessary to show the duration of protection against HPV infections in JDM patients and to assess the need for booster vaccinations. As there is no information in the literature regarding long-term protection in JDM patients, cervical smears should still be performed as secondary prevention of cervical abnormalities.

Conclusions

The HPV vaccination in juvenile dermatomyositis patients is safe and immunogenic. Since the seropositivity against HPV16 and HPV18 was very high after the 3-dose schedule, this regimen should be recommended for juvenile dermatomyositis patients.
Abbreviations

AEFV: adverse events following vaccination
AID: autoimmune diseases
CMAS: Childhood Myositis Activity Score
HC: healthy controls
HPV: human papillomavirus
JDM: juvenile dermatomyositis
MMT: Manual Muscle Testing
NIP: Brazilian National Immunization Program
qHPV: quadrivalent HPV vaccine

Declarations

Ethics approval and consent to participate
This study was approved by the Human Research Ethics Committee of the Ribeirão Preto Hospital das Clínicas and the Ribeirão Preto Medical School, SP, Brazil on July 21, 2014.

Consent for publication
A copy of the Informed Consent (for parents and legal guardians) and the Informed Consent (for healthy patients and controls) were given to the study participants and their guardians.

Availability of data and materials
Data sets generated and / or analyzed during the current study are available from the repository [ReBEC Brazilian Clinical Trial Registry], [http://www.ensaiosclinicos.gov.br/rg/RBR-9ypbtf/] and also are available from the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no conflicts of interest, including financial interests, activities, relationships, and affiliations to be disclosed in relation to this manuscript.

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**Authors’ contribution**

The PIs of this study were NBFP and GP. GSP, NBFP, and AL supervised the execution of the study in Brazil and coordinated the recruitment of patients and controls and the collection of clinical data and samples. FS, NEA, LBPM, SA, AGI, JOS, SKFO, BERGB, ACMF, TCMVR and CB assisted the collection of clinical data and samples. NBFP, NG, AL, and IHRG performed all data analyses and statistics. SR and GSP supervised data analyses and interpretation of the data. IHRG verified completed clinical data. HP and RS performed the laboratory analyses. FK and RS supervised the laboratory analyses. NG, SR, and IHRG wrote the initial drafts of the manuscript. NBFP and IHRG drew the figures and tables. NW initiated and supervised the project, data analysis, and writing of the manuscript. All authors read and approved the final version of the manuscript.

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Tables

**Table 1:** Baseline characteristics of the JDM patients and healthy controls.
JDM: Juvenile Dermatomyositis; n (%): total and percentage; NA: not applicable.

* Considering active disease for JDM: CMAS < 48.

** Heliotrope, rash and gottron.

*** Both disease activities: muscle and cutaneous involvement.

Table 2: Frequency of AEFV after the first, second and third doses of the qHPV vaccine in juvenile dermatomyositis patients and controls.
**Table 3.** Activity disease evaluation from JDM patients based on comparison of CMAS score and cutaneous involvement: heliotrope and rash at the baseline visit and visits after the second and third qHPV vaccine doses.

| Activity Disease | Comparison 1 | Comparison 2 | Comparison 3 |
|------------------|--------------|--------------|--------------|
| CMAS             | 0.38 / 0.27  | 0.21 / 0.46  | 0.30 / 0.63  |
| Heliotrope       | 0.92 / 0.79  | 0.54 / 0.44  | 0.81 / 0.70  |
| Rash             | 0.42 / 0.38  | 0.54 / 0.65  | 0.92 / 0.77  |

*p*-values McNemar Test and Kappa coefficient.
Figure 1

Flow diagram describing qHPV vaccine administration in JDM patients and HC individuals before and during the study. JDM: juvenile dermatomyositis; AEFV: adverse events following vaccine; HC: healthy controls.
Changes in Activity Disease

Comparison 1  Comparison 2  Comparison 3

CMAS

| Comparison 1 | Comparison 2 | Comparison 3 |
|--------------|--------------|--------------|
| 0            | 0            | 0            |
| 5.3          | 13.5         | 11.4         |
| 94.7         | 86.5         | 88.6         |

Rash

| Comparison 1 | Comparison 2 | Comparison 3 |
|--------------|--------------|--------------|
| 11.1         | 12.5         | 11.1         |
| 22.2         | 62.5         | 22.2         |
| 66.7         | 25           | 66.7         |
Activity disease evaluation from JDM patients based on comparison of CMAS score and cutaneous involvement: rash, gottron and heliotrope at the baseline visit and visits after the second and third qHPV vaccine doses. CMAS: Childhood Myositis Activity Score; Comparison 1: after two doses versus baseline; Comparison 2: after three doses versus baseline; Comparison 3: after three doses versus after two doses.
Figure 3

Flow diagram describing the serological analysis of JDM patients and HC individuals who received the second and third doses of qHPV vaccine. JDM: juvenile dermatomyositis; HC: healthy controls; HPV: human papillomavirus.

Forty-two JDM patients completed the 3-dose vaccination schedule, however blood samples were collected from only 36 patients after receiving the second dose, 31 after receiving the third dose, and 17 one year after receiving the first dose. Thirty-five HC individuals completed the 3-dose vaccination schedule; however, blood samples were collected from only 14 controls after receiving the second dose, and 31 after receiving the third dose.