Live-Attenuated Measles, Mumps and Rubella (MMR) and Varicella Zoster Virus (VZV) Vaccines Are Safe in Pediatric Patients with Juvenile Idiopathic Arthritis (JIA) Treated with Biologics

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Abstract

Juvenile Idiopathic Arthritis (JIA) broadly refers to a group of heterogenous diseases that share the common feature of chronic inflammatory arthritis of unknown cause lasting longer than 6 weeks with onset before 16 years of age [3]. Patients with autoimmune diseases such as JIA remain under-vaccinated due to hypothetical concern for infection development. However, it is crucial for these patients to be protected against vaccine-preventable illnesses due to their underlying immune dysfunction as well as the various immunomodulatory drugs that are used in its treatment. Current recommendations are out of date, as they clearly advise physicians to avoid giving these important vaccinations due to unsupported concerns that they are putting patients at risk of preventable death from infection arising from live vaccines. We performed a retrospective chart review and obtained data from patients via phone survey. Our results showed that the use of live-attenuated MMR and VZV vaccines is safe in pediatric patients with JIA being treated with biologics, as there were no serious adverse events reported.

Introduction

Juvenile Idiopathic Arthritis (JIA) broadly refers to a group of heterogenous diseases that share the common feature of chronic inflammatory arthritis of unknown cause lasting longer than 6 weeks with onset before age 16 years of age [3]. Patients with autoimmune diseases such as JIA remain under-vaccinated due to hypothetical concern for infection development. However, it is crucial for these patients to be protected against vaccine-preventable illnesses due to their underlying immune dysfunction as well as the various immunomodulatory drugs that are used in its treatment.

In the United States, the magnitude and number of measles outbreaks has increased, which has provoked a variety of policy changes aimed at improving vaccine coverage [5]. Phadke et al. reported that unvaccinated individuals continue to constitute a majority of cases in measles outbreaks. Additionally, they noted that in the context of the COVID-19 pandemic, immunization monitoring systems have identified marked reductions in the number of doses of measles-containing vaccine that have been ordered and administered. They highlighted the importance of having more data sources that can be used to make decisions about vaccine policy.

Regarding existing studies on vaccinations in children with rheumatic diseases, Toplak et al concluded that booster dose of live-attenuated vaccines in children treated with biologics was safe, but not always providing a protective immune response. In the last update on vaccinations in children with rheumatic diseases published in 2015, 15 studies including 296 patients treated with biologics were found [6]. A majority of these studied the use of non-live vaccines in children treated with biologics, and 4 studies investigated booster doses of live-attenuated vaccines among children treated with biologics. None of the patients in these studies had severe adverse events or autoimmune disease relapse after the vaccination. Prior to 2015, 4 studies of live-attenuated vaccination in children treated with biologic therapy were published; two of these studies investigated MMR vaccination in JIA patients, including 14 patients also receiving biologic therapy. Ten patients were treated with etanercept at the time of booster MMR, one with...
adalimumab and three with anti-IL1 therapy [2, 4]. There were no serious adverse events from vaccination.

Recently, live vaccine recommendations in Europe were updated at the 2017 European League Against Rheumatism-Pediatric Rheumatology European Society (EULAR-PReS) Task Force for Vaccination. PReS recommendation for live vaccines for pediatric patients was updated based on small case series and on expert opinion. Currently, they recommend that “vaccination with live-attenuated vaccines in patients on high-dose disease modifying anti-rheumatic drugs (DMARDs), high dose glucocorticosteroids (GCS) or biologic agents can be considered on a case-by-case basis, weighing the risk of infections against the hypothetical risk of inducing infection through vaccination [1,7].” Current Center for Disease Control (CDC) childhood vaccines guidelines recommend initiation of live vaccines (MMR and VZV) at one year, with a booster dose given between 4 and 6 years of age for immunocompetent children [8]. Per these guidelines, live vaccines are typically considered contraindicated in immunocompromised patients.

Considering that vaccine hesitancy and refusal by parents to vaccinate their children is on the rise and the concomitant increase in measles outbreaks, it is important for physicians to properly counsel parents to facilitate protection against these vaccine-preventable illnesses in this susceptible population.

**Specifically, our aim was:**

To provide retrospective evidence that MMR/Varicella live vaccines do not cause infections from exposure to the vaccine in patients with JIA being treated with biologics with or without methotrexate.

**Criteria for Subject Selection:**

Gender of subjects: equitable inclusion of males and females.

Age of subjects: Age 1-2 or 5-6 while being treated with a biologic, which are ages when children are usually vaccinated for MMR and Varicella.

Racial and Ethnic Origin: there will be no restriction on inclusion based on race or ethnic origin

Inclusion criteria: Juvenile idiopathic arthritis patients treated with adalimumab, canakinumab, etanercept, infliximab, tocilizumab, or abatacept, with or without methotrexate who received a live vaccine (MMR or VZV) while actively being treated.

Exclusion criteria: Any patient concurrently being treated with steroids or with active disease at time of vaccination.

**Methods And Procedures**

*Design*
This study consisted of a retrospective chart review using human subjects. Using CareCloud Electronic Medical Record (EMR) system, we generated a list of patients with ICD-10 diagnosis codes beginning with M08 and M25. Next, we called patients to obtain consent and administered a questionnaire including the following questions: Was your child being treated with a biologic (with description of both generic and brand names of drugs) at the time of their MMR or VZV live vaccines (with description of the current recommended guidelines regarding age given), if so which biologic? Do you recall any “mild adverse events” including any local skin reactions or systemic symptoms such as fevers, headache, body aches, generalized rashes, fatigue, etc? Do you recall any “serious adverse events” including development of measles, mumps, or rubella infection for MMR vaccine or chicken pox or varicella zoster infection from varicella vaccine, hospitalization following vaccine administration, or flare up of inflammatory arthritis following vaccine administration?).

**Data/results**

Our data showed that 20% (4) patients had a minor adverse reaction to the vaccine and 80% (16) had no adverse reaction to the vaccine. Patients were more likely to have mild adverse event vs serious adverse event with 100% (4/4) of the patients who reported having any reaction having mild adverse events vs 0% of the patients who had any reaction having a serious adverse event. These findings were significant with a P-value of 0.01391. 100% (2/2) patients who received Actemra had no reaction, 80% (4/5) patients who received Enbrel had no reaction, 77% (3/13) patients who received Humira had no reaction. However, due to small sample size, one cannot conclusively state if there is or is not a significant difference amongst Actemra, Enbrel, and Humira for vaccine reaction rates.

Due to small sample size, one cannot conclusively state if there is or is not a significant adverse reaction to live vaccines with methotrexate added to a biologic. However, 85% (17/20) patients had live vaccines with methotrexate, and 24% (4/17) of these patients had a minor reaction while 0% (0/3) patients who had live vaccines without methotrexate did not have a minor reaction. A larger sample size is needed to draw significant conclusions regarding methotrexate.

**Discussion**

The results of this study have provided further evidence that routine childhood vaccinations in children with JIA are safe. None of the patients in our study reported serious adverse events, including development of infection from the vaccines themselves and flare of patient’s existing autoimmune disease. More collective data regarding live vaccine administration in children with JIA treated with biologics is needed to draw further conclusions regarding concurrent use of methotrexate with biologics.

Potential limitations in our study included small sample size and the fact that our data was collected via retrospective chart review and phone survey, making recall bias possible.

**Conclusion**
In children with JIA who are being treated with biologics, routine live-attenuated MMR and VZV vaccines are safe and do not lead to development of vaccine-induced infection or flare of existing autoimmune disease. These findings should encourage pediatricians to allow and advise their patients who are treated with biologics to be vaccinated according to the American Association of Pediatrics (AAP) or CDC recommended schedule. Additionally, these findings should influence revision of current guidelines regarding use of live vaccines in certain children who are immunomodulated with biologic treatments.

**Abbreviations**

MMR: Measles, mumps, and rubella  
VZV: Varicella zoster virus  
JIA: Juvenile idiopathic arthritis  
DMARDs: Disease modifying anti-rheumatic drugs  
GCS: Glucocorticosteroid  
CDC: Center for Disease Control  
EULAR-PReS: European League Against Rheumatism-Pediatric Rheumatology European Society  
EMR: Electronic medical records  
AAP: American Academy of Pediatrics

**Declarations**

**Author Note:** We have no known conflicts of interest to disclose.

**Ethics Approval and Consent to Participate:**

This study went through IRB approval with WCG IRB; protocol number KAC3017. Patients consented over telephone to participate in a brief telephone survey.

**Consent for Publication:**

Consent was obtained using WCG IRB’s consent form and can be provided at reasonable request from corresponding author.

**Availability of Data and Materials:**

The datasets analyzed for this study are available at reasonable request from corresponding author.

**Competing Interests:**
The authors declare that they have no competing interests.

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**Author’s Contributions:**

MH (corresponding author, email: herre171@unlv.nevada.edu) was responsible for study design, performing retrospective chart review, and analyzed and interpreted the data. RL was the supervising physician and was a contributor in writing the manuscript. SL was responsible for performing the statistical analysis. All authors read and approved the final manuscript.

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**References**


