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Varicella Vaccination in Children With Inflammatory Bowel Disease Receiving Immunosuppressive Therapy

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Abstract

Children with inflammatory bowel disease (IBD) are often receiving chronic immunosuppressive therapy to stay in clinical remission; however, these therapies also put patients at risk for infections. Therefore, it is important to immunize children to minimize vaccine-preventable infections. However, there is a paucity of data on immune response to vaccines in patients with IBD. Current guidelines recommend that patients with IBD receive inactivated vaccines but suggest against immunizing immunosuppressed patients having IBD with live vaccines such as varicella. Unfortunately, the recommendation to not vaccinate with varicella was not based on any data. We present a case series of children with IBD receiving immunosuppressive therapy who tolerated and had a good immune response to varicella vaccine. We also review the literature and demonstrate that studies in other immunocompromised populations suggest that varicella vaccine is generally well tolerated and immunogenic. We also argue that it is important to weigh the benefits against risks with individual patients having IBD to decide whether varicella vaccination should be considered. Additional studies evaluating the safety and immunogenicity of varicella vaccine in patients with IBD are needed.

Keywords

immunization; immunosuppression; inflammatory bowel disease; vaccine; varicella

Patients with inflammatory bowel disease (IBD) often receive immunosuppressive therapy (eg, thiopurines, methotrexate, tumor necrosis factor inhibitors) for prolonged periods of time. Although such medications maintain remission and improve quality of life, they put patients at risk for infection. Therefore, it is important to implement preventive care, including immunizations to minimize the risk of vaccine-preventable infections.

In general, inactivated vaccines are considered to be safe in patients with IBD receiving immunosuppressive therapies. Two recent studies of the influenza vaccine demonstrated that the immune response in patients with IBD overall is good but that there may be a reduction in serologic response in patients receiving tumor necrosis factor inhibitors (1,2). However, there is a paucity of data regarding the immune response to the varicella vaccine in patients with IBD. Studies in other immunocompromised populations (eg, oncology, chronic renal failure, human immunodeficiency virus [HIV], transplant) show that varicella vaccine is generally well tolerated and immunogenic (3-12). We present a series of children with IBD

receiving immunosuppressive therapy who were injected with varicella vaccine, tolerated it without adverse events, and developed antibodies to the varicella virus.

CASE 1

A 20-year-old white female was diagnosed with ulcerative colitis in 1993 at age 4 years. After a severe exacerbation of ulcerative colitis at age 5, she was induced with tacrolimus and successfully transitioned to 6-mercaptopurine (6-MP) maintenance therapy. She had no history of chickenpox infection before the institution of therapy. At age 6, she was exposed to classmates with chickenpox in school. The family and gastroenterologist discussed the possibility of immunizing her with varicella vaccine, and it was decided that the benefits outweighed the risks. At the time of varicella immunization, the patient was receiving olsalazine and 6-MP ($1.8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$). She tolerated the vaccine without clinical manifestations of systemic or localized varicella. A baseline varicella titer was not drawn before vaccination. Thirteen years later, when she was about to attend college, she underwent testing to document immunity. The varicella-zoster IgG titer drawn at that time was 4.11 index value (IV). A value of less than or equal to 0.89 IV indicates negative immunity, and more than or equal to 1.10 IV indicates positive immunity.

CASE 2

A 6-year-old white female was diagnosed in 2006 at age 4 years as having Crohn disease involving the stomach, duodenum, and colon. She was induced with corticosteroid therapy and transitioned to 6-MP ($2.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) as maintenance therapy. She had received her initial dose of varicella vaccine in 2003, before her diagnosis of Crohn disease. After her diagnosis and while receiving immunosuppression, she was exposed to classmates with chickenpox on 2 occasions. A baseline varicella-zoster IgG titer was drawn after the first exposure in October 2006, and was 0.37 IV (consistent with absent immunity). The patient received a course of acyclovir after both exposures without adverse events. After the second course of acyclovir in August 2007, the family decided to immunize her with varicella vaccine after weighing the benefits of protection against the risk of the vaccine. No adverse events or clinical manifestations of varicella were noted. A follow-up varicella IgG titer drawn 3 weeks after vaccination was 1.39 IV (consistent with the development of immunity to the varicella).

CASE 3

A 15-year-old white male was diagnosed at age 9 years in 2002 as having Crohn ileitis. He was given 6-MP shortly after diagnosis. Five years later, the family inquired about the varicella vaccine, given the patient's chronic immunosuppressed state. He was vaccinated with the primary varicella dose at age 6 years. A baseline varicella titer was not drawn. After a discussion of risks versus benefits, the family decided to immunize the patient with varicella booster to prevent him from developing wild-type varicella in the setting of immunosuppression. He was receiving 6-MP ($1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), mesalamine, and ciprofloxacin at the time of vaccination. He tolerated the varicella booster without clinical manifestations of varicella. The follow-up titer was 0.90 IV (equivocal immunity).

CASE 4

An 11-year-old white male was diagnosed in 2007 at age 10 years as having Crohn disease involving the stomach, duodenum, and ileum. His symptoms persisted despite 1 month of mesalamine. Therefore, it was decided to start immunosuppressive therapy with 6-MP ($1.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$). The patient had previously received 1 dose of the varicella vaccine,

but did not receive the booster. Therefore, he was given the varicella booster 1 day before the institution of the 6-MP therapy. A varicella IgG titer drawn on the day of the booster was 1.42 (positive immunity). He tolerated the booster without clinical manifestations of varicella.

CASE 5

A 13-year-old Hispanic female received her initial dose of varicella vaccine at age 4 years. Subsequently, she was diagnosed in 2004 at age 8 years as having Crohn disease of the ileum. She was induced with prednisone and maintained on 6-MP, but subsequently had active disease and required the institution of infliximab in October 2005. She was maintained in clinical remission with infliximab (5 mg/kg every 8 weeks) and mesalamine. In 2007, at the age 12 years, the patient was inadvertently given a booster of varicella vaccine at her primary care physician's office, without consideration that she was receiving infliximab. No adverse reactions or clinical manifestations of varicella were reported after vaccination. A baseline varicella titer was not obtained before the booster, but a follow-up titer obtained demonstrated immunity to varicella (2.41 IV).

CASE 6

A 14-year-old white female was given her primary dose of varicella vaccine at age 5 years. She was later diagnosed in March 2007 at age 13 years as having Crohn disease involving the stomach, duodenum, ileum, and colon. Because of persistent disease activity, she was given infliximab 6 months later. In April 2008, while receiving both infliximab and 6-MP, she was also inadvertently immunized with varicella vaccine at her primary care doctor's office. She did not experience any adverse reactions or clinical manifestations of varicella. A baseline varicella titer obtained when the patient was initially seen in our gastrointestinal clinic, which was 6 months before vaccination, was 0.88 IV (negative immunity). The follow-up titer 9 weeks after vaccination was 2.41 IV (positive immunity).

DISCUSSION

We have described a series of cases in which children with IBD receiving immunosuppressive therapy tolerated varicella vaccine and demonstrated antibody response. The majority of the patients in our case series received the primary varicella vaccine before the diagnosis of IBD and the booster vaccine after diagnosis. We acknowledge the possibility that some patients, in whom a baseline serology was not obtained, may have had subclinical varicella disease or developed an adequate antibody titer after the primary varicella vaccine, to explain the high antibody titer found after the booster.

Although routine immunization of immunosuppressed patients with IBD with inactivated vaccine (eg, influenza, meningitis) is an accepted practice, there remains considerable uncertainty about the appropriateness of immunizing with varicella vaccine. One published expert-panel document (13) suggested not immunizing patients with IBD receiving immunosuppressive therapy with the live attenuated varicella vaccine. Unfortunately, these recommendations were based on anecdotal and uncited reports of complications after measles-virus vaccination in immunocompromised non-IBD populations. The panel even stated in this document that "in patients with leukemia on long term 6-MP therapy, the varicella vaccine was well tolerated in most patients, and would be expected to be equally safe in patients with IBD on azathioprine or 6-MP (13)." The reason that this panel advised against the administration of varicella vaccine in this population is unclear, but could reflect anxiety about the potential of vaccine-associated complications.

Current recommendations to administer or hold vaccines are based on expert opinion rather than published data; however, recommendations vary from 1 expert panel to the other. For example, the 2008 Advisory Committee on Immunization Practices suggests that the zoster vaccine (which is similar to but 14 times more potent than the varicella vaccine) may be safely given to adults with IBD or certain rheumatologic conditions receiving less than or equal to $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of azathioprine, less than or equal to $1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of 6-MP, or less than or equal to $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$ of methotrexate. In addition, the recommendations of the Advisory Committee on Immunization Practices state that the zoster vaccine can be administered by the patients who are receiving short-term or low-dose of immunosuppressive therapy (14). Thus, the recommendations differ from those of the IBD expert panel. These recommendations also leave a number of questions unanswered, specifically:

1. What constitutes “low-” versus “high” -dose immunosuppressive therapy?
2. How long should immunosuppressive therapy be held before the administration of live vaccine?
3. If live vaccine is administered, when should immunosuppressive therapy be started?
4. Is there a difference between primary immunization (first dose of varicella vaccine) and a booster dose (in someone who may already have memory B cells primed to respond)?
5. Is there a different benefit/risk ratio in immunizing children (who are more likely to be exposed to wild-type disease) than adults?

Studies on immune response to live vaccines administered to other types of immunosuppressed children (eg, oncology, chronic renal failure, HIV, transplant) suggest that many of these patients tolerate live vaccines and produce a good immune response (3-12). In a landmark study of the varicella vaccine, Gershon et al (3) immunized with either 1 or 2 varicella vaccine doses 437 children with leukemia who were in remission. Eighty-eight percent of all of the children seroconverted after 1 vaccine dose and 98% after 1 or 2 vaccine doses. Four patients developed fever with a severe rash suggestive of varicella (500–1000 lesions, some of which were hemorrhagic), and 1 patient had pneumonia. Acyclovir was given and all of the patients responded. There were 42 fatalities in the study, which were all due to leukemia and were not associated with the vaccine or varicella. Yeung and colleagues (4) vaccinated 17 children having acute lymphoblastic leukemia and 2 children having non-Hodgkin lymphoma who were in remission on maintenance chemotherapy. The seroconversion rate was 68%. Seven children developed either rash or fever within 7 to 53 days (median 24 days) after vaccination. One patient developed varicella 11 months after vaccination. These children were compared with a control arm consisting of 117 unvaccinated patients with leukemia or lymphoma who were in remission on chemotherapy. The crude incidence was 1.25 cases of varicella per 100 person-years in the vaccinated group, compared with 11.67 cases per 100 person-years in the control group. In addition, 1 patient in the control group died of varicella pneumonia and encephalopathy. Another small study (5) in 17 children with malignancies also demonstrated a >90% seroconversion rate after the second vaccine dose. There was 1 vaccine-associated rash requiring acyclovir.

The findings in oncology populations expand to other populations with chronic illness. Patients with chronic renal failure are often immunosuppressed. Furth et al (6) vaccinated 50 children who had chronic renal failure and no detectable varicella-zoster virus antibody. The patients were immunized with 2 doses of varicella vaccine, and 48 of 50 seroconverted after the first dose. There were no reports of disseminated varicella. Two studies also suggest that

it is safe in patients with HIV infection at clinical stage N or A (asymptomatic or mildly asymptomatic) and immunological stage 1 (CD cell count normal for age) (7,8).

Most patients receiving transplantation develop antibody protection after immunization even if they are receiving immunosuppressive therapy. Although some cases of vaccine-associated rash have been reported, there have been no cases of disseminated vaccine-associated disease. Kano et al (9) immunized pediatric patients before liver transplantation with the measles, mumps, rubella, and varicella vaccines and found that the seroconversion rates were 82% to 100%. The investigators revaccinated patients at least 1 year posttransplantation if their antibody titers waned and found the seroconversion rates were 71% to 100%. There were no adverse effects or serious illnesses reported. Weinberg et al (10) found that approximately 85% of liver and intestine transplant recipients receiving immunosuppressive therapy (tacrolimus, sirolimus, cyclosporine, corticosteroids) had an adequate immune response after receiving varicella vaccine. A vesicular rash appeared in one quarter (4/16) of subjects within 1 to 24 days after vaccination; 3 of these 4 children received oral acyclovir, and lesions healed within 1 to 7 days in all 4 subjects. Chaves et al (11) immunized 6 pediatric patients with renal transplantation undergoing different immunosuppressive regimens (including mycophenolate, tacrolimus, azathioprine, cyclosporine, and/or prednisone) who had a varicella antibody titer <500 mAU/mL with varicella vaccine. Sixty-seven percent (4/6) of patients mounted an adequate immune response (varicella-zoster virus antibody titer >500 mAU/mL) by 6 to 8 weeks postvaccination. None of the patients had an adverse reaction or developed skin lesions (11). Zamora and colleagues immunized 34 children receiving chronic dialysis or who had a renal transplant (taking prednisone, cyclosporine, azathioprine) who had a negative varicella antibody with varicella vaccine. Eighty-five percent of the patients (29/34) developed IgG titers >1:40 within 6 months postvaccination. Three renal transplant recipients developed a mild form of varicella within 2 to 4 years after vaccination (12).

We hope the case series and literature review presented in this article prompt additional discussion of the potential of varicella vaccine in children with IBD. Patients with IBD often receive immunosuppressive treatment throughout childhood, a time when varicella exposures are common. Although no complications from varicella vaccine have been reported in patients with IBD, there have been reports of major complications from wild-type infection (15-19). It is ironic that the use of corticosteroids and immunomodulators places children with IBD at serious risk for disseminated wild-type varicella infection, yet the 1 published immunization guideline recommends against vaccinating these patients without any data (13).

In summary, there are no current data on the safety and immune response to varicella vaccination in patients with IBD receiving immunosuppressive therapy. The case series of 6 patients that we present show that these children tolerated the varicella vaccine, and all but 1 patient was found to have positive immunity after vaccination. In our opinion, the risk of wild-type varicella infection in immunosuppressed patients with IBD is not negligible. Therefore, it is important to weigh the benefits against risks with individual patients with IBD to decide whether varicella vaccination should be considered. In some cases (eg, high-dose immunosuppression, corticosteroids) the risk of vaccine-associated varicella may outweigh the risk of wild-type varicella infection and its complications. However, many younger children with IBD are receiving low-dose immunosuppression (eg, 6-MP) and have been previously immunized. In these children who undergo frequent exposure to wild-type varicella in the community, the benefit of immunization may outweigh the risk. Additional studies evaluating the safety and immunogenicity of varicella vaccine in patients with IBD are clearly needed to provide additional data for guideline committees (Table 1).

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TABLE 1

Patients' immune and clinical response to varicella vaccination

Patient	Primary vs booster vaccine received	Age at primary vaccination, y	Age at booster vaccination, y	Medications at time of varicella vaccination	Baseline IgG varicella titer (IV)	Follow-up IgG varicella titer (IV)*	Adverse reaction
1	Primary	6	—	Olsalazine, 6-MP	None obtained	4.11	None
2	Booster	1	5	6-MP	0.37 after primary dose	1.39	None
3	Booster	6	14	6-MP, mesalamine, ciprofloxacin	None obtained	0.90	None
4	Booster	In early childhood	10	To start 6-MP 1 day after vaccination	None obtained	1.42	None
5	Booster	4	12	Infliximab, mesalamine	None obtained	2.41	None
6	Booster	5	14	Infliximab, 6-MP	0.88 after primary dose	4.64	None

IV=index value; 6-MP = 6-mercaptopurine.

* A value of 0.89 IV indicates negative immunity, and 1.10 IV indicates positive immunity.