

Should my patient with inflammatory bowel disease on immunosuppressive therapy be vaccinated against influenza virus?

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Crohn's disease and ulcerative colitis are variants of inflammatory bowel disease (IBD) for which immunosuppressive therapy is often required. Immunosuppressed patients are at increased risk for infections, including vaccine-preventable diseases such as influenza. Although several guidelines recommend routine influenza immunization for such patients, recent literature suggests that this patient population may be inadequately immunized. Current research suggests that inactivated influenza vaccines are effective, well tolerated and can be administered safely in most IBD patients. Studies in other immunosuppressed populations have also demonstrated the safety of inactivated vaccines. The present article reviews the literature regarding the safety and efficacy of influenza vaccination in IBD patients receiving immunosuppressive therapy.

Key Words: *Crohn's disease; Immunization; Inflammatory bowel disease; Influenza; Ulcerative colitis; Vaccination*

Crohn's disease and ulcerative colitis are both variants of inflammatory bowel disease (IBD), and affect approximately 0.5% of Canadians (1). Disease onset can occur at any age but typically peaks in the third decade of life (1). It is generally accepted that an unknown environmental agent(s) and a dysfunctional mucosal immune system in genetically susceptible individuals leads to the development of either Crohn's disease or ulcerative colitis (2). Treatment of IBD often requires the use of immunosuppressive medications including corticosteroids, purine antimetabolites, methotrexate and newer biological agents (eg, infliximab, adalimumab, certolizumab and natalizumab). As a result of immunosuppression, patients with IBD may be at higher risk for certain infections than the general population and the outcomes of these infections may be more severe (3,4).

The risk of influenza infection and its complications is considered to be higher in patients undergoing immunosuppressive therapies (5). Influenza is an acute respiratory infection from which most people recover. However, adults and children with chronic illnesses such as IBD are at greater risk for severe complications such as pneumonia and death (6). Depending on the severity of the virus in any given season, between 2000 and 8000 Canadians die of influenza and its complications annually (6). Whether immunocompromised patients are more susceptible to a novel virus such as the pH1N1 (swine) strain is

Mon patient atteint d'une maladie inflammatoire de l'intestin qui prend des immunosuppresseurs devrait-il être vacciné contre le virus de l'influenza ?

La maladie de Crohn et la colite ulcéreuse sont des variantes des maladies inflammatoires de l'intestin (MII) souvent traitées au moyen d'immunosuppresseurs. Les patients immunosupprimés sont plus vulnérables aux infections, y compris des maladies évitables par un vaccin comme l'influenza. Même si plusieurs lignes directrices recommandent la vaccination systématique contre l'influenza chez ces patients, de récentes publications indiquent que cette population ne serait pas suffisamment vaccinée. Selon les recherches à jour, les vaccins contre l'influenza inactivé sont efficaces, bien tolérés et peuvent être administrés en toute sécurité à la plupart des patients atteints d'une MII. Des études auprès d'autres populations immunosupprimées démontrent également l'innocuité des vaccins inactivés. Le présent article contient une analyse des publications au sujet de l'innocuité et de l'efficacité du vaccin contre l'influenza chez les patients atteints d'une MII sous immunosuppresseurs.

unknown and is beyond the scope of the present review. Infections, including those of the upper respiratory tract, increase the risk of exacerbations of gastrointestinal symptoms in IBD patients (7).

Influenza is one of the most common vaccine-preventable illnesses in adults (8), and annual vaccination of immunosuppressed patients has been recommended by several agencies (5,8-10). Recent guidelines from the European Crohn's and Colitis Organisation (11) recommend routine influenza vaccination of all IBD patients, including those on immunomodulators. Both a live attenuated vaccine and a trivalent inactivated vaccine (TIV) are available for seasonal influenza, but only a TIV is recommended for patients who are immunosuppressed (5). Live attenuated vaccines were not licensed in the United States until 2003. They are administered via nasal spray and are only recommended for healthy, nonpregnant persons between two and 49 years of age (12). TIV preparations have been available since the 1940s and are administered via intramuscular injection, and can be given to anyone older than six months of age (12). The composition of the TIV is reviewed annually and changed based on the anticipated strains of seasonal influenza A or B (13). The seasonal TIV recommended for the 2009 to 2010 season is not effective against pH1N1.

TIVs for seasonal influenza are effective in preventing laboratory-confirmed influenza illness. Randomized, placebo-controlled

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trials conducted in children and healthy adults demonstrate 70% to 90% efficacy in preventing influenza infection (14). The inactivated influenza vaccine may be less effective in patients receiving immunosuppressive medications (15,16). Although there are limited data on the efficacy of influenza vaccination in IBD patients, several guidelines recommend the vaccination of patients with chronic disease, including those with IBD who are immunosuppressed (5,8-10). The present article reviews the current literature pertaining to the efficacy and safety of seasonal influenza vaccinations in IBD patients receiving immunosuppressive therapy.

METHODS

Literature search

A systematic search was conducted to retrieve high-quality, peer-reviewed studies of influenza vaccination in IBD. The PubMed, Medline and EMBASE databases were searched with text ("vaccination", "influenza", "colitis", "Crohn" and "inflammatory bowel disease") and MeSH terms ("Crohn's disease", "ulcerative colitis", "inflammatory bowel diseases", "influenza vaccination" and "immunization"). Results were limited to English language publications.

DISCUSSION

Vaccination use in patients with IBD

Melmed et al (17) surveyed 169 IBD patients to assess their immunization histories and exposures to known risk factors for influenza, *Streptococcus pneumoniae*, viral hepatitis and varicella. The majority of these patients (86%) reported current or previous use of immunosuppressive medications. Only 41 patients (24%) reported receiving regular influenza vaccinations. The most common reasons for nonimmunization with influenza vaccines were lack of awareness (49%) and concern for side effects (18%).

The findings of the Melmed et al study were consistent with reports of influenza vaccination in other at-risk populations. Sowden and Mitchell (18) found that only 53% of patients on immunosuppressants who were attending outpatient rheumatology clinics in the United Kingdom had received influenza vaccinations. Bridges et al (19) reported that only 56% of patients receiving methotrexate for rheumatoid arthritis (RA) were immunized against influenza. The most commonly cited reason for nonimmunization was 'never being offered the vaccine'. These data suggest that patients and health care providers are not aware of national immunization guidelines or have residual concerns about the risk-benefit trade-off in special patient populations.

Efficacy of vaccination in IBD

To date, few studies have assessed the immune response to influenza vaccine in patients with IBD (Table 1). Mamula et al (15) assessed 51 pediatric IBD patients and 29 healthy controls undergoing single-dose inactivated influenza vaccination. The authors used hemagglutinin inhibition (HI) titres of 1:40 or higher as a measure of the vaccine efficacy, which is considered to have better correlation with influenza protection than other methods (20). Overall, the immune response to the B/Hong Kong vaccine antigen was reduced (62% versus 89%; $P=0.0125$) (15). Among patients receiving infliximab and immunomodulatory therapy, responses to two of the three influenza vaccine antigens were reduced (63% versus 95% for

strain A/New Caledonia/20/99, $P=0.018$; and 33% versus 89% for strain B/Hong Kong/330/2001; $P=0.002$). However, no other significant differences were observed and the vaccine was well tolerated by the test group. Only 15 patients (19%) reported adverse events, all of which were mild, including soreness at the injection site (14%), having a cold (5%), influenza-like symptoms (4%) and headache (1%). Furthermore, vaccination did not affect the clinical activity of IBD as measured by the Pediatric Crohn's Disease Activity Index for patients with Crohn's disease, and by the Lichtiger Colitis Activity Index for patients with ulcerative colitis. Although serological conversion in patients with IBD on concomitant infliximab and immunomodulatory therapy may be inadequate, the authors recommended routine immunization for patients with IBD because of good tolerability.

During the 2007 to 2008 influenza season, Lu et al (21) conducted a prospective cohort study of the efficacy of inactivated influenza vaccine in 137 pediatric IBD patients. They obtained serum from these patients to determine a baseline influenza titre, immunized the patients with a TIV, then remeasured titres three to nine weeks later. HI titres of 1:40 or greater were used to define seroprotection. They found that regardless of immunosuppressive status, more patients attained seroprotection against strains A/Solomon Islands/3/2006 (H1N1) and A/Wisconsin/67/2005 (H3N2) than the B/Malaysia/2506/2004 strain. Overall, rates of seroprotection were not affected by the use of immunosuppressive therapy; however, a subanalysis showed that those receiving antitumour necrosis factor (TNF) therapy were less likely than those on no immunosuppression to be protected against strain B (14% versus 39%; $P=0.025$). Responses in the IBD study cohort were similar to those in a comparator cohort of healthy controls. Similar to Mamula et al (15), the authors found the vaccine to be well tolerated, with no effect on disease activity. Lu et al (21) also recommended routine influenza vaccination for IBD patients.

Gelinck et al (22) assessed the serological responses to influenza vaccine in 112 patients receiving anti-TNF therapy, including 22 with IBD. They found no significant difference in the rates of seroprotection (HI titre greater than 1:40) among patients who were treated with anti-TNF agents and patients treated with either other immunosuppressive medications or healthy controls. However, the absolute level of titres against two influenza strains was significantly lower in the anti-TNF group. The authors noted no differences in vaccine efficacy with respect to underlying disease or anti-TNF agent. No major side effects or exacerbations of disease were reported.

While all of the studies were consistent in their definition of seroprotection as HI titres of greater than 1:40, humoral response is only a surrogate marker for an immunoprotective state. It would be preferable to monitor patients for the development of influenza infection after receiving a TIV.

Influenza vaccination in other immunosuppressed populations

Many transplant recipients do not receive an annual influenza vaccination, largely because of physicians' concerns about triggering an allograft rejection (23). Hypothetically, non-specific immune activation following vaccination may lead to enhanced cellular or humoral responses against donor organs; there are anecdotal reports of acute rejection subsequent to

TABLE 1

Prospective studies of immune response to influenza vaccination in patients with inflammatory bowel disease (IBD)

Author (reference)	Study design	Intervention	Outcome(s) measured	Result
Mamula et al (15) 2007	Prospective cohort study with 51 IBD patients and 29 controls	Administration of influenza vaccine	Primary: HI before and 4 weeks after vaccination. Seroprotection was HI \geq 1:40 at 4 weeks. Secondary: Safety and clinical disease activity (measured by CDAI or LCAI)	IBD patients had lower seroconversion to 1 of 3 strains. Patients on both infliximab and immunomodulators were less likely to convert 2 of 3 strains than healthy controls. Vaccine was safe and well tolerated
Lu et al (21) 2009	Prospective cohort study with 137 IBD patients and 76 controls	Administration of influenza vaccine	Seroprotection (defined as HI \geq 1:40 to each influenza strain measured 3 to 9 weeks postvaccination), absolute antibody titres and adverse events	Most IBD patients attained seroprotection regardless of immunosuppressive therapy (especially to A strains). Patients on anti-TNF therapy were less likely to be protected against the B strain. Vaccine was safe and well tolerated
Gelinck et al (22) 2008	Prospective cohort study with 112 patients on anti-TNF therapy (including 22 with IBD) and 18 controls	Administration of influenza vaccine	HI before and 4 weeks after vaccination, seroprotection defined as HI \geq 1:40	No significant difference in proportion of individuals attaining a protective titre (HI \geq 1:40) but absolute titre levels lower in patients on anti-TNF therapy. Vaccine was safe and well tolerated

CDAI Crohn's Disease Activity Index; HI Hemagglutinin inhibition titre; LCAI Lichtiger Colitis Activity Index; TNF Tumour necrosis factor

immunization (19). However, most studies have failed to demonstrate a definitive association between influenza vaccination and graft rejection (24-29). Burbach et al (30) and Lawal et al (31) observed no increase in rejection or liver enzyme elevation after influenza vaccination among 62 and 51 liver transplant recipients, respectively. Candon et al (23) found no increased risk of allograft rejection, as measured by antihuman leukocyte antigen antibody serum levels within 30 days of vaccination among 66 stable renal transplant recipients. Kimball et al (32) reported no excess rejection, no increase in alloantibodies and no changes in lymphocyte subpopulations among 29 vaccinated heart transplant recipients. In the largest study to date, White-Williams et al (33) also found no increase in rejection among 3601 heart transplant recipients who received an influenza vaccination. This study revealed that transplant institutions enforced varying intervals between transplantation and vaccination, but that this interval did not appear to affect rates of rejection.

Similar concerns about increased immune activity have tempered the enthusiasm for vaccination in patients with autoimmune disease (34). A review by Elkayam (35) identified several small trials in which influenza vaccination induced an adequate humoral response without inducing a clinical exacerbation of RA; however, their cumulative sample size was too small to draw any definitive conclusions.

More recently, Oren et al (36) compared the safety and immunogenicity of influenza vaccine in 14 RA patients on rituximab with 29 patients on other nonbiological disease-modifying antirheumatic drugs. No significant worsening of any clinical or laboratory parameter of disease activity was noted in either group of patients, but those on rituximab mounted lower humoral responses (21% versus 67%; $P=0.006$). Salemi et al (37) assessed the development of seroprotective titres against influenza over three consecutive influenza seasons by administering influenza vaccination to healthy control subjects and 28 patients with stable RA who were undergoing anti-TNF treatment. Their study revealed that the RA patients did not develop clinical or biochemical disease reactivation with vaccination but were less likely to develop seroprotection against the influenza B strain. Kaine et al (38) assessed humoral

responses to influenza and pneumococcal vaccination in a double-blind trial comparing adalimumab ($n=99$) with placebo ($n=109$) in patients with RA. In subjects without protective antibody titres at baseline, antibody responses were similar in the adalimumab and placebo groups (73.3% and 73.9%, respectively). Rates of disease flare, adverse events and treatment discontinuation were also similar. Overall, evidence supports the use of influenza vaccine in RA patients who are on immunosuppressive medication.

Serious adverse reactions to influenza vaccine

The most common adverse events associated with inactivated vaccines are arm soreness and redness at the injection site (39). These are mild reactions and generally resolve within two days. Systemic symptoms such as fever, arthralgia and malaise occur much less frequently, and are more likely to occur in individuals exposed to the vaccines for the first time (12). Guillain-Barré syndrome (GBS) is a rare neurological condition that was associated with the 1976 swine influenza vaccine at a rate of one per 100,000 persons vaccinated (40). Since then, some studies have estimated its incidence with seasonal influenza vaccine at one per million persons vaccinated, and others (41,42) have not found an association between influenza vaccination and GBS. The Advisory Committee on Immunization Practices (5) recently stated that the potential benefits of influenza vaccination in preventing serious illness, hospitalization and death outweigh the possible risk of vaccine-associated GBS. Influenza vaccines should not be given to individuals who have had an anaphylactic reaction to a previous dose or with a known immunoglobulin E-mediated hypersensitivity to eggs that manifests as swelling of the mouth and throat, hypotension, difficulty breathing or shock (13). Patients with serious acute febrile illnesses should not be vaccinated until their symptoms have resolved (13).

Observational data have raised concerns about the reactivation of IBD with influenza vaccination, but the overall quality of these data is poor. Kwan et al (43) reported on a 39-year-old woman with ulcerative colitis who was well controlled on oral mesalazine, who experienced abdominal pain and frequent bowel movements with hematochezia three days after

vaccination, but responded to steroid induction. Another case report (44) describes a 52-year-old woman with ulcerative colitis who had been in remission without steroids for nine months; however, within hours of receiving an influenza vaccination, the woman experienced a severe exacerbation of her disease that could not be controlled with steroids and immunosuppressive medications. She became steroid-dependent, experienced many corticosteroid-induced side effects and, finally, underwent a total colectomy within three months. The patient subsequently recalled milder reactivation following a previous influenza vaccination.

CONCLUSIONS

Patients with IBD are at risk for the same vaccine-preventable illnesses as the general population. Influenza is one of the most common vaccine-preventable illnesses, but patients with IBD often fail to receive appropriate immunizations because of poor awareness and uncertainty about vaccine safety and efficacy (17). This may have significant consequences for patients taking immunosuppressive medications because they are the most vulnerable to serious complications from infection. The limited available data suggest that these patients can achieve protective titres, albeit less often than healthy controls, with good safety. Two reports of disease reactivation are insufficient reason to withhold immunization. However, physicians should administer vaccines with caution to patients with previous adverse reactions to the vaccine. Further prospective studies are needed to clarify the benefits and risks of immunization in patients with IBD.

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