Alimentary Pharmacology & Therapeutics

Review article: influenza A (H1N1) virus in patients with inflammatory bowel disease

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Publication data
Submitted 13 September 2009
First decision 23 September 2009
Resubmitted 1 October 2009
Accepted 1 October 2009
Epub Accepted Article 1 October 2009

SUMMARY

Background
Infection with influenza A (H1N1)*v* (swine flu) has caused widespread anxiety, among patients who are potentially immunocompromised, such as those being treated for inflammatory bowel disease.

Aim
To provide guidance for physicians and their patients on the risk, prevention and management of influenza A (H1N1)*v* infection.

Methods
Medline was searched using the following key words: 'swine flu', 'immunosuppression', inflammatory bowel disease', 'recommendations', 'immunization', 'vaccination'. Organizations such as European Centre for Disease Prevention and Control, the Centers for Disease Control and Prevention and the World Health Organization were consulted for recent papers and recommendations regarding immunocompromised patients and influenza A (H1N1)*v* infection.

Results
Pandemic influenza A (H1N1) virus predominantly affects young patients. Those who are immunocompromised because of underlying disease or treatment are considered at higher risk of complications from influenza A (H1N1). They should be offered prevention (vaccination, postexposure prophylaxis) or treatment with antiviral drugs, if affected. Pneumococcal infection is a complication of influenza infection; therefore, pneumococcal vaccination appears advisable. Seasonal influenza vaccination is also recommended. Withdrawal of immunosuppressive treatment appears advisable during severe active infection if possible.

Conclusions
Pragmatic advice is the best that can be offered in the current circumstances because of paucity of evidence. Investigation into the impact of influenza A (H1N1)*v* infection in young people with chronic conditions is needed.

doi:10.1111/j.1365-2036.2009.04161.x

INTRODUCTION

On April 2009, the Centers for Disease Control and Prevention (CDC) identified two cases of human infection with influenza A (H1N1)*v* characterized by a unique combination of gene segments that had not been identified among human influenza A virus.[1] Additional cases were rapidly reported leading the WHO to declare a pandemic phase level 6, indicating widespread human infection. This has caused widespread anxiety, especially among patients who are potentially immunocompromised and symptoms of serious systemic infection may be wrongly attributed to influenza A (H1N1)*v*.

Most cases of influenza A (H1N1)*v* currently seem to have uncomplicated influenza-like illnesses; the most common symptoms are cough and fever. Calculating the case fatality ratio related to influenza A (H1N1)*v* is highly dependent on estimates of the total number of people with the disease, which are not easy to obtain. Nevertheless, on the basis of surveillance data and mathematical modelling, the influenza A (H1N1)*v* case fatality ratio seems to be higher than that of seasonal influenza, although it remains of the same order of magnitude.[2, 3] The severity and deaths associated with seasonal influenza infection result in a large part from secondary complications such as secondary bacterial pneumonia (*Streptococcus pneumonia or Staphylococcus aureus*), primary viral pneumonia and exacerbation of underlying chronic conditions.[4, 5] Initial observation suggests that children and young adults may be more susceptible to influenza A (H1N1)*v* than older persons.[6] It is still unclear whether the low incidence in people over 60 years of age is because of a partial immunity from former infections with H1N1 influenza viruses. Although the median age among the persons who died of influenza A (H1N1)*v* is lower than those who die of seasonal influenza, when infection does occur, the percentage of deaths in the elderly seems to be higher than in other age groups.[2, 3] Pregnant women and patients with underlying conditions such as respiratory disease, cardiac disease, diabetes, obesity, or immune suppression are commonly reported in hospitalized cases and are considered at higher risk of complications.[2, 6, 7] Patients with inflammatory bowel disease (IBD) are in large part of younger age and may be immunocompromised because of their treatment. Immunomodulators commonly used in IBD are corticosteroids, azathioprine, methotrexate, calcineurin inhibitors, anti-tumour necrosis factor agents or other biologics, all compromising, to some extent, the patient's immune response. For this reason, they might be considered as susceptible to and at high-risk from complications of novel influenza (H1N1) virus infection. In this article, we provide guidance for physicians on the risk, prevention and management of influenza A (H1N1)v infection in patients with IBD. This reflects expert opinions and may complement national guidelines when available. Medline was searched using the following key words, individually and in combination: 'swine flu', 'immunosuppression', 'inflammatory bowel disease', 'recommendations', 'immunization',' vaccination'. The European Centre for Disease Prevention and Control, the CDC and the World Health Organization were consulted for recent papers and recommendations regarding immunocompromised patients and influenza A (H1N1) virus infection. No definitive national guidelines are available at the time of writing.

In this particular setting, strategies for care providers to prevent disease occurrence and its complications in IBD patients rely on general precautions to limit inter-human transmission of the virus and the use of a vaccination against influenza A (H1N1)*v,* as well as the use of pneumococcal polysaccharide vaccine. Post-exposure antiviral chemoprophylaxis is best implemented in specific situations and treatment of the influenza A (H1N1)*v* infection best adapted for patient with IBD (Table 1).

STRATEGIES TO PREVENT INFLUENZA A (H1N1)*V* INFECTION IN PATIENTS WITH IBD:

Personal protective measures for reducing the risk of acquiring or transmitting human influenza do not differ for IBD patient than for the large public. Measures for self protection are mainly (i) avoid close contact with sick people, (ii) wash hands frequently and (iii) avoid touching his own eyes, nose or mouth.[8] Additional details are available on the European Center for Disease Control website: http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx.

Prevention of influenza is usually achieved by vaccination. New vaccines directed towards the influenza A (H1N1)*v* infection are currently being manufactured. Two recent studies have shown reassuring data regarding the efficacy and safety of these novel vaccine, whether in an MF59-adjuvant form or not, in young and middle-aged adults.[9, 10] These data are

Table 1. Strategies to prevent influenza A (H1N1) occurence and its complications in IBD patients.

Clinical circumstances	Standard IBD	IBD on immunomodulators*
Vaccination against H1N1	In line with general recommendations	Yes
Vaccination against seasonal influenza virus	In line with general recommendations	Yes
Vaccination with pneumococcal polysaccharide vaccine	Yes†	Yes
Asymptomatic patient with IBD, exposed to or in close contact with H1N1 influenza virus	Measures for self-protection	Measures for self-protection Neuraminidase inhibitors (e.g. oseltamivir 75 mg daily) for 10 days
Patient with IBD and symptoms of mild‡ flu	Measures to protect family and close contacts No treatment	Measures to protect family and close contacts Neuraminidase inhibitor (e.g. oseltamivir 75 mg twice daily) for 5 days§
Patient with IBD and symptoms of severe flu	Measures to protect family and close contacts Neuraminidase inhibitors (e.g. oseltamivir 75 mg twice daily) for 5 days§ Take specialist advice	Measures to protect family and close contacts Neuraminidase inhibitors (e.g. oseltamivir 75 mg twice daily) for 5 days§ Temporarily withdraw IM Take specialist advice

* Immunomodulators used in inflammatory bowel disease are corticosteroids, azathioprine, methotrexate, calcineurin inhibitors, anti-tumour necrosis factor agents, or other biologics. For corticosteroids, doses of prednisone ≥20 mg/day for more than 2 weeks are considered as an immunomodulator.
† According to Rahier *et al.*[18]
‡ Defined as uncomplicated febrile illness, with systemic symptoms, but no respiratory distress or prostration.
§ In patients on multiple immunomodulators who are considered to be severely immunosuppressed, higher doses of oseltamivir may be considered, because of the risk that resistant strains may emerge. Likewise, longer treatment duration may be considered because of longer viral shedding in severely immunosuppressed patients[24].

difficult to extrapolate to adults who have underlying immune suppression, which is the group for whom the influenza A (H1N1)*v* vaccine is particularly recommended.

However, data on influenza A (H1N1)*v* vaccination may be extrapolated from the seasonal influenza vaccine. The efficacy of influenza vaccination depends on the ability of a person's immune system to respond adequately to vaccine antigen. Immune dysfunction can potentially compromise vaccine response and effectiveness. Two studies have, however, shown that immunocompromised patients with IBD generally have an adequate response rate to influenza vaccination.[11, 12] An adequate response is observed in patients with rheumatic diseases, except for those on biological therapies, which may diminish the response to influenza vaccination.[13] Interestingly, vaccination on the day of anti-TNF administration might facilitate seroconversion.[14] Although influenza vaccination (non-live vaccine) appears to be safe in the immunocompromised, the lack of safety data on vaccines against the novel influenza A (H1N1) virus in patients on immunomodulators means that the safety and efficacy of these vaccines should be continuously monitored.

Patients with IBD on immunomodulators or biological therapy are best advised to receive the appropriate vaccine as soon as it is available, following national guidelines on vaccination against influenza A (H1N1)*v*.[15] Recommendations regarding influenza A (H1N1)*v* vaccination may differ by country, according to the amount of vaccine available, the type of vaccine used, the particular epidemiology and practical considerations. The European Medicines Agency (EMEA) has very recently recommended the authorization of two vaccines (Focetria, Pandemrix) for influenza pandemic (H1N1) 2009. Additional information can be found on the following website: http://www.emea.europa.eu/

influenza.home.htm. The US Advisory Committee on Immunization Practices recently recommended the administration of influenza A (H1N1) 2009 monovalent vaccine in patients with immunosuppression caused by medication.[16] Those patients not on immunomodulators or biological therapy are not believed to be immunocompromised and should be considered in line with the general population.

Pandemic influenza A(H1N1)v virus is likely to become the predominant circulating influenza virus as it has been demonstrated in New Zealand and Australia.[7, 17] As a result, patients with IBD on immunomodulators or biological therapy are best advised to receive the appropriate vaccine against influenza A (H1N1)*v* as soon as it is available. Seasonal influenza vaccine does not protect against influenza A (H1N1)*v* infection.[17] However, seasonal influenza vaccination should take place as usual in immunocompromised patients with IBD[18] because of the potential of co-circulation of other influenza strains along with A(H1N1)v.[17] Pneumococcal vaccination could reduce the complication rate from influenza A (H1N1)*v* infection in high risk groups. Vaccination recommendations for all patients with IBD include pneumococcal polysaccharide vaccine, with repeat vaccination at 5 years.[19] Pneumococcal vaccination should be implemented regardless of H1N1 vaccine availability.

POSTEXPOSURE ANTIVIRAL CHEMOPROPHYLAXIS

The currently circulating influenza A (H1N1)*v* is sensitive to neuraminidase inhibitors: oseltamivir (Tamiflu) and zanamivir (Relenza). Patients with IBD on immunomodulators or biological therapy who are close contacts of persons with confirmed or probable cases of novel influenza A (H1N1) virus infection should receive postexposure antiviral chemoprophylaxis with either oseltamivir (75 mg daily) or zanamivir (two inhalations of 5 mg daily). Antiviral chemoprophylaxis should be initiated within 48 h after the last known exposure to the novel (H1N1) influenza and continued for 10 days after the last known exposure to novel (H1N1) influenza.[20, 21] The use of neuraminidase inhibitors during pregnancy must depend on advice from a specialist in infectious diseases. Pre-exposure antiviral therapy should not be considered in patients with IBD. In practice, it may prove impractical to deliver appropriately timed postexposure prophylaxis to the majority of our patients with IBD.

STRATEGIES FOR TREATING SUSPECTED OR CONFIRMED INFLUENZA A (H1N1)*V* INFECTION IN PATIENTS WITH IBD

In the event of infection, the first measures are to protect family members and other close contact by (i) maintaining good respiratory hygiene, (ii) washing hands frequently and (iii) staying at home.[8] IBD patients who are receiving immunomodulators or biological agents and who meet current case-definition for confirmed or probable cases novel influenza A (H1N1) virus infection should be treated with antiviral drugs: oseltamivir (75mg twice daily), or zanamivir (two inhalations of 5mg twice daily),[20] as they are at high risk of complications from influenza. The drugs should be given within 48 h and the earlier the better. However, some data from studies on seasonal influenza indicate benefit for hospitalized patients even if treatment is started more than 48 h after onset. Neuraminidase inhibitors have been shown to reduce complications associated with influenza, including the need for antibiotics.[21, 22] Although evidence is lacking, it seems sensible temporarily to withdraw immunomodulator therapy at least during the symptomatic phase of infection and probably until 24 h after symptoms and signs of fever have resolved. As patients not on immunomodulators are not considered high risk, there is no need for antiviral treatment for uncomplicated influenza A (H1N1)*v* infection. On the other hand, a severe or progressive clinical presentation should promptly be treated with antiviral therapy, with advice from an infectious diseases' specialist, regardless of their IBD or immunocompromising condition.[23] For patients on multiple immunomodulators who are considered to be severely immunosuppressed, higher doses of oseltamivir may be considered, because of the risk that resistant strains may emerge. Likewise, longer treatment duration may be considered, because of longer viral shedding in severely immunosuppressed patients.[24] There is no known interaction between neuraminidase inhibitors and drugs used in IBD, although methotrexate plasma levels may increase with concomitant use of oseltamivir, as both drugs use similar metabolic excretion pathways. *In vitro* studies, however, suggest a minimal effect and no clinical consequence for those on low doses of methotrexate, such as those used in IBD.[25] It is particularly important that clinicians do not overlook conventional infection or inflammatory conditions that may mimic the symptoms of pandemic flu, because such an oversight may have severe consequences.

CONCLUSION

As Gastroenterologists, we believe that it is our responsibility to motivate our patients to receive immunization and make sure that those measures are part of our management plan; otherwise, our patients will be left unprotected. We believe that the opportunity should be taken to vaccinate against pneumococcal infection and that seasonal influenza vaccination should be performed as normal for those on immunomodulators.[18] In the event of suspected infection with influenza A (H1N1)*v* in an immunocompromised person, or clinically serious infection in anyone with IBD, prompt antiviral treatment is appropriate. The situation is rapidly evolving and recommendations may change, but this appears the most practical advice at present.

MAIN POINTS

(i) Patients with IBD and treated with immunomodulators are at high-risk from complications of novel influenza (H1N1) virus infection.

(ii) General precautions to limit inter-human transmission of the virus should apply to all IBD patients regardless of their immune status.

(iii) Patients with IBD and treated with immunomodulators should receive vaccinations against seasonal influenza, H1N1 virus and pneumococcal polysaccharide vaccine. Vaccination in immunocompetent patients with IBD should follow general recommendations.

(iv) Postexposure chemoprophylaxis usefully mitigates infection when used at an early stage in immunosuppressed patients.

(v) Severe or progressive clinical infection with influenza A (H1N1)*v* should be treated with antiviral therapy, with advice from an infectious diseases' specialist, regardless of their IBD or immune status.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

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