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Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease

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Abstract

Background and aims: Appropriate influenza vaccination is important for patients with inflammatory bowel disease under immunosuppressive therapy. The purpose of this study was to evaluate the influence of immunosuppressive therapy on the immune response to the trivalent influenza vaccine in adult patients with inflammatory bowel disease.
Methods: In this cohort study, 91 participants received a single dose of influenza vaccine for the 2010/2011 season. Serum samples were collected at 3 different times (pre-vaccination, 3 weeks post-vaccination, and after flu season) to measure hemagglutination inhibition antibody titers. Immune responses were compared based on immunosuppressive therapy.
Results: Among the 88 subjects who completed the study, the influenza vaccine induced a more than 4-fold increase in the mean antibody level for all flu strains. The overall seroprotection proportion (post-vaccination titer $\geq$ 1:40) was 81% for H1N1, 61% for H3N2, and 86% for B. Treatment with an immunomodulator reduced the immune response to the H1N1 strain (OR = 0.20, p = 0.01), and treatment with infliximab reduced the immune response to the

Abbreviations: AZA, azathioprine; CAI, clinical activity index; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; GMT, geometric mean titer; HAI, hemagglutination inhibition; IFX, infliximab; IS, group immunosuppressive group; 6MP, 6-mercaptopurine; NIS, group non-immunosuppressive group; OR, odds ratio; SD, standard deviation; UC, ulcerative colitis; WHO, World Health Organization.

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other strains (H3N2 strain: OR = 0.37, $p = 0.02$; B strain: OR = 0.18, $p = 0.03$). Combination therapy with azathioprine/6-mercaptopurine and infliximab significantly inhibited the immune response to H1N1 (OR = 0.056, $p = 0.02$).
Conclusions: Infliximab and/or immunomodulators inhibit immune responses to some strains of trivalent influenza vaccination in adults with inflammatory bowel disease. For optimization of the trivalent influenza vaccination for patients with adult inflammatory bowel disease treated with immunosuppressive agents, establishing an effective vaccination method is crucial.

1. Introduction

Inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD) are accompanied by chronic inflammation of the gastrointestinal tract due to a complex interplay between environmental factors, dysregulated immune systems, and genetic susceptibility.[1] Immunosuppressive (IS) therapeutics such as immunomodulators or anti-tumor necrosis factor-α (TNF-α) agents are frequently used as aggressive therapies for IBD. However, immunosuppressive agents such as systemic corticosteroids, azathioprines (AZA)/6-mecaptopurine (6-MP), tacrolimus, methotrexate, and anti-TNF-α agents (e.g., infliximab [IFX]) increase the risk for more frequent and severe infections in IBD patients.[2–4] Combination therapies using more than one IS agent are especially associated with increased risk for opportunistic infections,[5] including bacterial and many severe and fatal viral infections.[6–8] Recent publications recommend more appropriate vaccination strategies for IBD patients as infection prophylaxis prior to IS therapy.[9,10]

Influenza, caused by type A or type B viruses, is a prevalent respiratory illness that can lead to other associated complications and hospitalization. Influenza patients often seek medical attention in hospital emergency rooms, and absence rates for workers and students increase dramatically during the influenza season.[11] In the US, approximately 226,000 patients are hospitalized annually for influenza, and approximately 36,000 cases of influenza-related deaths are reported each year.[12,13] In 2009, the World Health Organization (WHO) reported of the human infection with influenza A(H1N1). HIN1 spread rapidly throughout the world during the 2009/2010 influenza season, leading WHO to declare a phase 6 pandemic alert.[14] Epidemiologic studies for the pandemic outbreak in 2009 revealed that the risk of influenza-associated complications for adults infected with influenza A(H1N1)pdm09 was higher than usual for seasonal influenza.[15]

Several recent studies that examined the immunogenicity of the influenza A(H1N1)pdm09 vaccine in IBD patients[16–23] have cautioned that combination therapy with anti-TNF-α agents and immunomodulators (AZA/6MP) may reduce the immune response to vaccines.[17,18] Similar findings have been reported for the trivalent influenza vaccine, which is routinely distributed as a seasonal influenza vaccine.[16,22,24] These reports also showed that children undergoing IS therapy for IBD exhibited reduced immune response to the vaccine. To the best of our knowledge, however, no studies have reported the effect of IS therapy on the specific immune response to the individual strains covered by the trivalent influenza vaccine in adults with IBD. Although adults are generally considered to generate a better immune response to the vaccine than children do, it is important to examine the effect of IS therapy in adult IBD patients. Therefore, the aim of the present study was to investigate the immune response to the trivalent influenza vaccine in adult IBD patients undergoing IS treatments.

2. Materials and methods

2.1. Subjects

We conducted this prospective, open label, cohort study from September 2010 to July 2011 in the Department of Gastroenterology at Osaka City University Hospital. Between 29 September 2010 and 14 October 2010, IBD outpatients (minimum age, 20 years) were recruited for participation in the study.

The exclusion criteria were as follows: patient had already received 2010 trivalent inactivated influenza vaccine; patient had history of influenza infection within the last 6 months; patient had history of anaphylactic reaction to previous influenza vaccine or vaccine components or of acute febrile illness or signs of severe acute illness at the time of vaccination. All participants provided written, informed consent following a detailed explanation of the nature and possible consequences of the study. All participants in the study signed informed consent forms. We estimated the appropriate sample size was 100 participants for the present study based on the reference of the guidance of the European Committee for Proprietary Medical Products.[25] The study protocol was approved by the Ethics Review Board of the Osaka City University Graduate School of Medicine.

2.2. Data acquisition

At the time of recruitment, we obtained the following patient information from the medical records: defined disease (ulcerative colitis [UC] or Crohn's disease [CD]); disease duration; current IS therapy (corticosteroids, tacrolimus, AZA, 6-MP and IFX), which has been continued for more than 3 months; and data from blood tests (white blood cell count, differential leukocyte count, serum albumin, hematocrit, C-reactive protein). All medications were required to be stable prior to vaccination and for at least 3 weeks after vaccination. Validated clinical activity scores, clinical activity index (CAI) of Rachmilewitz index,[26] and Crohn's disease activity index (CDAI),[27,28] were used to assess disease activity in patients with UC and CD, respectively. A CAI score of ≥ 5 for UC and a CDAI score of >150 for CD were defined as active