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Influenza and Pneumococcal Vaccination and Varicella Status in Inflammatory Arthritis Patients

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Abstract
Patients with inflammatory arthritis are at increased risk of vaccine preventable infections. This risk is increased by immunomodulatory therapies. Vaccination for influenza and pneumococcal disease reduces the risk. Severe cases of varicella infection have occurred in patients on biologic therapies. We sought to identify vaccination rates for commonly acquired infections and to ascertain varicella immune status in patients with inflammatory arthritis. 100 patients with inflammatory arthritis were administered a standardised questionnaire. Data collected included age, diagnosis, vaccination history, history of varicella, treatment and the presence of other indications for vaccination. 58 patients (58%) had not received the influenza vaccine in the past year. Only 19 patients (19%) had ever received pneumococcal vaccine. Anti TNF use did not predict vaccination (p=.46). An increasing number of co morbid conditions predicted both pneumococcal (p<0.003) and influenza vaccine (p<0.03) administration. Nineteen patients (19%) gave no history of varicella infection, none having had varicella titres checked pre treatment. Immunisation rates in patients with inflammatory arthritis on immunosuppressive therapies are low. Immunisation schedules should be available for each patient during rheumatology and general practice consultations.

Introduction
Inflammatory arthritis sufferers have higher rates of infection compared to the general population¹. Their underlying immune dysregulation, co-morbid conditions and treatment with steroids and anti-TNF agents contribute to this risk². Disease modifying therapies (DMARDs), in particular methotrexate, have not been demonstrated to increase the risk of infection³. The most common infections in patients with rheumatic diseases involve the respiratory tract, with bacterial infection accounting for the majority⁴. Streptococcus pneumoniae is the pathogen in approximately 50% of cases of community acquired pneumonia⁵. Vaccination against influenza and pneumococcal disease is safe in patients with rheumatic diseases on immunosuppressants and international guidelines recommend their routine use^{6,7}. In Ireland, national guidelines for vaccination identify nine adult â at riskâ groups, which include patients with immunosuppressive conditions such as B- and T-cell disorders, HIV infection and leukaemia. Rheumatological conditions are not specifically mentioned, though chronic renal, heart, lung and liver disease are⁸. Vaccine adherence has received greater attention in the rheumatology literature in the past number of years due to increased immunomodulatory effects of therapies and increasing awareness of the infection risk. The expectation was that this would lead to increased vaccination uptake in rheumatology clinic attendees.

The incidence of primary varicella zoster (VZV) infection in adults is increasing⁹. Disease complications are greater in adults¹⁰. Immunosuppressive therapy is a risk factor for poorer outcome and complications following primary varicella infection. There are several case reports in patients on anti-TNF agents¹¹. Immunosuppressive therapy also increases the risk of reactivation of latent disease. Immunity can be confirmed by testing for VZV IgG in serum and subsequent vaccination of non-immune patients may reduce morbidity and mortality. We undertook a study in patients attending our clinic to identify 1) influenza and pneumococcal vaccination uptake in patients with inflammatory arthritis and 2) varicella titres/history of chickenpox in the same cohort.

Methods
Patients with a diagnosis of inflammatory arthritis attending their out-patient appointment at the rheumatology clinic in St James Hospital, Dublin were surveyed from June - August 2008. Patients were eligible for inclusion if they were taking corticosteroids and/or disease modifying agents, either alone or in combination with anti TNF therapy. The physician enquired about influenza and pneumococcal vaccination over the past five years and past history of chickenpox/shingles using a standardised questionnaire. Other data collected included age, gender, rheumatological diagnosis, location of vaccination, vaccine prescriber, current treatment and the presence of co-morbid conditions that were indications for vaccination. The questionnaire had previously been validated in two other immunocompromised patient populations¹². Serum was tested for VZV IgG in patients unsure of their history of chickenpox. Formal approval was obtained from the hospital ethics committee. Statistical analysis was conducted using SPSS.18.0

Results
Baseline demographics/medications and co morbid conditions
One hundred patients with a mean age of 59.6 years (range 18-82years) were interviewed. Demographic data and rheumatological diagnoses are shown in Table 1. Fifty four patients (54%) had separate indications for vaccination of which age over 65 was the most frequent (Table 1).

Rates of influenza vaccine
Forty-two patients (42%) had received the influenza vaccine in the past year. 48 patients (48%) had never received the influenza vaccine (Figure 1). In those on anti TNF therapy 56 (56%) had not received the seasonal flu vaccine in the previous year. Anti TNF usage did not predict increased likelihood of receiving influenza vaccine (p=0.46). Those over the age of 65 were significantly more likely to have received influenza vaccine from their GP in the past year than those under 65 (p<0.01).

*Combination DMARD = Combination of Methotrexate, Salazopyrin and/or Hydroxychloroquine

Figure 1: 5 Year Influenza vaccine uptake

Rates of pneumococcal vaccine
81 patients (81%) of those surveyed had never received a pneumococcal vaccination. Only 7 patients (7%) had both an initial vaccine and a subsequent booster at 5 years as recommended in immunocompromised patients¹³ (Figure 2). Pneumococcal vaccine uptake was not increased in patients on anti TNF agents compared to those on other immunosuppressant regimes (p=.526). Age greater than 65 did not predict pneumococcal vaccine uptake. The presence and increasing number of co morbid conditions predicted both pneumococcal (p<0.003) and influenza vaccine(p<0.03) administration.

Rates of varicella zoster exposure
81 patients (81%) gave a history of prior exposure to varicella zoster, considered to be sufficient evidence of prior infection. 19 patients (19%) were unsure of their exposure history including nine patients on anti TNF therapy. Varicella Zoster Virus (VZV) IgG levels were negative in four of the 19 patients (21%) including one on anti TNF therapy. VZV levels had not been checked in any of the patients prior to commencing treatment.

Figure 2: Lifetime Pneumococcal vaccine uptake

Vaccination advice

5% of patients (3/60) who had received a vaccination had done so following recommendation from a hospital doctor. None had done so following consultation with their rheumatologist. Most had either sought the vaccine of their own accord or received it following counselling from their GP.

Discussion

Despite increased emphasis on vaccinations in the rheumatology literature, immunisation rates in this cohort are sub-optimal. The figures reported are similar to previous reported studies in European countries¹⁴. Given the increased susceptibility to infection amongst patients with inflammatory arthritis and the potential to reduce this risk with influenza and pneumococcal vaccination^{15,16}, it is important to ensure that current education and immunisation guidelines are being implemented. One of the major barriers to improved vaccine uptake is lack of recommendation by doctors¹⁸. A majority of patients report they would take a vaccine if their doctor recommended it¹⁷. In this study, primary care was the commonest source of recommendation. Younger rheumatology patients without other medical conditions may rarely interface with primary care and in this study were less likely to be vaccinated. Patients with inflammatory arthritis who had co existing ischaemic heart disease or chronic obstructive airways disease had higher rates of vaccination. This suggests arthritis may be ignored as an indication for vaccination unless another indication is present, despite evidence showing that it reduces morbidity and mortality from influenza and pneumonia in such patients. Patients on anti-TNF therapy were not more likely to be vaccinated than those on less immunosuppressive regimes. This is of concern as those most susceptible to infection¹⁹ and most likely to benefit are not being identified by care providers.

The ultimate responsibility for vaccine adherence lies with the prescriber of the immunosuppressive therapy and therefore efforts to improve vaccine adherence need to be lead by secondary care physicians. Strategies that engage secondary care providers to improve vaccination uptake need to be examined. As influenza vaccination is seasonal, extra resources should be made available in clinics for the 6-8 week period post immediate availability of seasonal influenza vaccine prior to onset of the influenza season. As the vaccine itself is free this would mean the recruitment of extra staff to administer the vaccine in clinics. Given that booster pneumococcal vaccination need only be repeated after a 5 year period, resources should be targeted at patients attending hospitals in one particular year in an effort to improve vaccination rates. This strategy was successfully applied in diabetic patients resulting in a rise of vaccination uptake from 26% to 60%²⁰.

In larger hospitals the creation of chronic inflammatory diseases assessment clinics (CIDAC) are an option. These clinics, led by the infectious disease service, would provide advice on vaccination to all specialties that have patients at risk of infection through their underlying inflammatory disease or its treatments. The provision of a vaccine passport²¹ would form part of this clinic. Treatment would be commenced when all vaccinations were up to date as approved by the infectious disease physician. At subsequent rheumatology clinic reviews this passport could then be examined to ensure vaccine compliance was satisfactory. The role of rheumatology nurse specialists to increase vaccine adherence should be further explored especially in the context of education sessions prior to commencing any immunosuppression. Systems could also be put in place that remind both patients and providers of the need for vaccination. A recent American lead task force found strong evidence that provider reminder systems (electronic prompts/alerts or stickers on paper charts) are effective¹⁸. In particular SMS texting to announce the availability of influenza vaccine may be practical and cost effective as means of a reminder system.

Although many vaccines are provided free of charge the responsibility for ensuring vaccine adherence predominantly lies with individual primary or secondary care health professionals. On a national level vaccination uptake should be included as a quality measure of any programme prescribing immunosuppressants given the demonstrable evidence that vaccination reduces subsequent health care costs in this vulnerable population. The inclusion of vaccination uptake as a nationwide quality assurance measure for departments would strengthen individual services requests for extra resources and funding to ensure improved service provision.

Ireland does not have a national vaccination programme for varicella zoster and so patients remain at risk of primary infection. In Ireland ICGP/HPSC data from 2000-2005 revealed that 17% of cases occur over age 15 years. In tropical regions less than 60% of adults are immune²¹. As the population of Ireland changes a more vulnerable group of patients is entering the health care system. Patient reported history of varicella exposure can be considered evidence of immunity²². In individuals unsure of their exposure history, a number will be non-immune as demonstrated in our study. Reports of fatal varicella infection in patients on immune-suppressive therapy²³ underscore the importance of accurate identification of those at risk. Varicella IgG levels should be checked in all patients who are unsure of their exposure history. The lack of history and/or serological evidence of infection should prompt providers to immunise these individuals before initiation of immune-suppressive treatments. Secondary reactivation of VZV is also an important issue. Although the outcome of primary disease is worse the burden of secondary (reactivation) disease is greater in the Irish population. Patients, in particular those on anti TNF regimes, and providers should be educated on the role of early introduction of antiviral medication. Furthermore Zostervax, a live vaccine has recently²⁴ been demonstrated to reduce the severity and duration of herpes zoster infection.

Inflammatory arthritis is a strong indication for influenza and pneumococcal vaccination but uptake remains suboptimal. A significant minority of patients remain at risk of primary varicella infection. A more proactive role needs to be taken by the health professionals prescribing immunosuppressive therapy for these high-risk patients in an effort to reduce the morbidity and mortality associated with infection. Further studies are required of secondary care physiciansâ attitudes toward vaccination and its perceived importance in the outpatient consultation. Vaccination status should be incorporated in the routine review of patients attending the rheumatology clinic and efforts to improve vaccine adherence should be coordinated via the rheumatology clinic. Furthermore, use of vaccination uptake within rheumatology departments as a quality measure may ensure improved resource allocation for this goal. Novel strategies including use of vaccine passports, SMS texting and the creation of inflammatory disease assessment clinics need to be considered.

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