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Risk of solid organ transplant rejection following vaccination with seasonal trivalent inactivated influenza vaccines in England: A self-controlled case-series

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ABSTRACT

Background: Annual seasonal influenza vaccination is recommended for transplant recipients. No formal pharmacoepidemiology study has been published on the association between solid organ transplant (SOT) rejection and vaccination with seasonal trivalent inactivated influenza vaccines (TIIVs).
Methods: The risk of SOT (liver, kidney, lung, heart or pancreas) rejection after TIIV vaccination was assessed using a self-controlled case-series method (NCT01715792). SOT recipients in England with transplant rejection were selected from the Clinical Practice Research Datalink and linked Hospital Episode Statistics inpatient data. The study period (September 2006 to August 2009) encompassed three consecutive influenza seasons. We calculated the relative incidence (RI) of SOT rejection between the 30- and 60-day post-vaccination risk periods and the control periods (any follow-up period excluding risk periods), using a Poisson regression model.
Results: In seasons 2006/07, 2007/08, 2008/09 and pooled seasons, 132, 136, 168 and 375 subjects, respectively, experienced at least one transplant rejection; approximately half (45%–51%) of these subjects had received a TIIV. For season 2006/07, the RI of rejection of any organ, adjusted for time since transplantation, was 0.74 (95% CI: 0.24–2.28) and 0.58 (95% CI: 0.24–1.38) during the 30-day and 60-day risk periods, respectively. Corresponding RIs for season 2007/08 were 1.21 (95% CI: 0.55–2.64) and 1.31 (95% CI: 0.69–2.48); for season 2008/09, 0.99 (95% CI: 0.43–2.28) and 0.64 (95% CI: 0.31–1.33); and for pooled seasons 1.01 (95% CI: 0.58–1.76) and 0.88 (95% CI: 0.56–1.38). The results of a separate analysis of kidney rejections and analyses that took into account additional potential confounders were consistent with those of the main analyses, with 95% CIs including 1 and upper limits below 3.
Conclusion: This study provides reassuring evidence of the safety profile of TIIVs in SOT recipients, thus supporting current recommendations to vaccinate this risk group annually.

1. Introduction

Compared to the general population, individuals with a compromised immune system are at increased risk of medical complications following influenza virus infection [1]. Solid organ transplant (SOT) recipients are a notable high-risk immunosuppressed population [2]. Influenza virus infection can cause substantial morbidity and mortality in SOT recipients and can trigger acute rejection and chronic allograft dysfunction [3–7]. Consequently, annual seasonal influenza vaccination is recommended for transplant recipients and their close contacts as an important preventative health measure [8].

Although influenza vaccination is generally well tolerated in SOT recipients [9], there is a paucity of robust and conclusive

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; GP, general practitioner; HES, Hospital Episodes Statistics; NHS, National Health Service; RI, relative incidence; SCCS, self-controlled case-series; SOT, solid organ transplant; TIIV, trivalent inactivated influenza vaccine; WHO, World Health Organization.

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evidence regarding the risk of acute cellular and humoral rejection episodes or allograft dysfunction following influenza vaccination [1,2,4]. Several spontaneous case reports in the published literature have suggested a possible association between SOT rejection or early signs of rejection among transplant recipients who had received influenza vaccination during the 2009 H1N1 pandemic influenza [10–12]. One case of pancreas rejection was reported and a small case-control study identified six cases of short-term cellular rejection among heart transplant recipients shortly following receipt of pandemic influenza vaccination during the 2009 H1N1 pandemic [10,11]. De novo anti-HLA antibodies were found in kidney transplant recipients who had received both seasonal and pandemic influenza immunization [12].

In view of these spontaneous case reports and following sporadic post-marketing surveillance reports of SOT rejection after receipt of GSK's monovalent AS03 (Adjuvant System containing α-tocopherol and squalene in an o/w emulsion) adjuvanted 2009 H1N1 pandemic vaccine (*Pandemrix*™, GSK Vaccines, Wavre, Belgium), a post-authorization safety study (PASS) was requested by the European Medicines Agency to assess the risk of SOT rejection following vaccination with *Pandemrix*™ in the 2009/2010 pandemic influenza season. These results have been reported elsewhere [13]. An additional objective of this study, which is the subject of the present manuscript, was to assess the risk of SOT rejection after immunization with seasonal trivalent inactivated influenza vaccines (TIIVs). Although annually-updated TIIVs have been routinely administered to SOT recipients for several years, no formal pharmacoepidemiology study of their use had been conducted in this patient group. In this study, the risk of organ rejection after vaccination with TIIVs was assessed among SOT recipients who experienced a transplant rejection in England during three consecutive influenza seasons.

2. Methods

In this retrospective, observational database study (ClinicalTrials.gov, NCT01715792), we assessed the risk of SOT (liver, kidney, lung, heart or pancreas) rejection within 30 and 60 days following the receipt of TIIVs using the self-controlled case-series (SCCS) method. This statistical case-only method compares the incidence rate of an event during predefined risk and control periods within a given individual, thereby controlling for individual level confounding factors that do not vary over time [14]. The study period spanned from 1 September 2006 to 31 August 2009, encompassing three consecutive influenza seasons (2006/07, 2007/08 and 2008/09).

The Clinical Practice Research Datalink (CPRD), an observational and interventional research service that operates as part of the UK Department of Health, contains over 4 million active patient records (over 11 million overall) drawn from approximately 675 primary care practices in the UK [15,16]. The population of active patients represents 7% of the total UK population, and CPRD patients have been shown to be representative of the UK general population in terms of age, sex and ethnicity [16]. The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages including Hospital Episode Statistics (HES) and Office for National Statistics mortality data. The work of CPRD is also covered by the National Information Governance Board for Health and Social Care's Ethics and Confidentiality Committee approval ECC 5-05 (a) 2012. This study was endorsed by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research.

2.1. Subjects and data collection

Cases were identified from patients registered in general practices contributing to the CPRD and with a linked HES inpatient component [17–19] using pre-defined algorithms. The CPRD contains coded longitudinal medical records from general practices in the UK [17] and the HES inpatient database contains details of all admissions to National Health Service (NHS) hospitals in England [19,20]. HES inpatient data linkage is limited to CPRD research-acceptable patients with a valid NHS number, living in England and who belong to a general practice that has agreed to take part in data linkage.

Subjects were eligible for this study if they received a liver, kidney, lung, heart or pancreas transplant and experienced at least one episode of transplant rejection during the study period. Subjects were defined as acceptable for research by the CPRD if they had no follow-up interruptions and information on year of birth, first registration date and gender, and if the data were considered to be of good quality, according to data quality assessments performed by the CPRD team [16]. The study dataset was built using the 2012 third quarter CPRD release, which compiled information from 10,547,532 subjects, with a mean follow-up of 6.8 years, from 644 general practices.

Records of transplantation and transplant rejection events were identified using pre-defined algorithms based on READ codes in the CPRD and ICD-10 clinical and OPCS-4 procedural codes in the HES linked component (Supplementary Table 1). Multiple transplant rejection episodes for a single individual were considered as new only if they occurred at least 30 days after the previous record of transplant rejection, apart from heart rejections, for which all episodes were considered as distinct events. A transplantation episode in an individual was considered as new if reported by OPCS-4 procedural codes or if it occurred more than 14 days since the previous transplant episode.

CPRD code lists for influenza vaccination were developed by querying the CPRD database for relevant product and influenza immunization terms and by using British National Formulary therapy group 14040900 (Supplementary Table 2). The influenza virus strains included in the licensed TIIVs were based on the annual World Health Organization (WHO) recommendations for the Northern Hemisphere [21]. Information on the TIIV brands administered was available for only 10%, 20% and 12% in each of the seasons 2006/07, 2007/08 and 2008/09, respectively.

In order to obtain additional quantitative and qualitative information on identified cases, a standard questionnaire (Supplementary Text 1) was sent to general practitioners (GPs) via the CPRD Research Group in October 2012.

2.2. Statistical analyses

Sample size was estimated for the primary objective of the study (i.e., to assess the risk of SOT rejection following vaccination with *Pandemrix*™ in the 2009/2010 pandemic influenza season) using relevant information and defined assumptions based on feasibility data (Supplementary Text 2). We found that, with 30 cases, there was 80% power to detect a relative incidence (RI) of 3 or higher. The association between SOT rejection and seasonal vaccination with TIIVs was assessed by calculating the RI of SOT rejection between the 30-day and 60-day post-vaccination risk periods and the control periods, with associated 95% confidence intervals (CIs). The 30-day risk period was defined a priori, based on the observed latency period of spontaneous rejection events reported to GSK's Global Clinical Safety and Pharmacovigilance among subjects who had received *Pandemrix*™ and the most common risk period following other exposures such as infection [3]. The case series model is derived from a Poisson cohort model by conditioning on the total

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