**NCT number: NCT02936180**

**Study title: Improving Influenza Immunization Responses in Rheumatoid Arthritis: A Strategy To Enhance Protection Against A Preventable Cause Of Death In An At Risk Population?**

**Date 26 August 2016**

***Executive Summary***

**Improving influenza immunization responses in rheumatoid arthritis: comparison of standard versus high dose inactivated trivalent influenza vaccine**

**1. Overview**

Four hundred and ten adults diagnosed with seropositive rheumatoid arthritis (RA) will be recruited to a randomized, observer-blind study of standard dose quadrivalent- versus high dose trivalent- inactivated influenza vaccine (SD-QIV vs. HD-TIV respectively) over two consecutive influenza seasons (Year 1: 2016-17/ Year 2: 2017-18). Each year, 205 patients will be stratified according to RA treatment and randomized 1:1 to receive either a single IM dose of a SD-QIV (FLUZONE® Quadrivalent Influenza Vaccine) or a single IM dose of a HD-TIV (FLUZONE® High Dose Influenza Vaccine). Both vaccines are produced by Sanofi Pasteur and are approved by Health Canada for immunization of immunocompromised patients. The primary study outcomes will be the immunogenicity of HD-TIV relative to SD-QIV at 28 days using standard serologic criteria. Secondary and exploratory outcomes will include induction of influenza-specific cellular responses at 28 days, persistence of antibody and cellular responses at 6 months, safety and the frequency of clinical events (i.e. pneumonia and health care utilization) in HD-TIV relative to SD-QIV recipients.

**2. Sponsor, Investigator, Study Site**

Sponsor

| | |
|---|---|
| Kate Lee, PhD-MBA | Michael D. Decker, MD, MPH |
| VP, Research | Vice President and Global Medical Expert |
| The Arthritis Society | Sanofi Pasteur |
| *Operating Grant* | *Provision of Vaccines* |

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**3. Study Objectives**

1) Primary objective

- To determine if the HD-TIV improves immune responses compared to SD-QIV in people with RA using standard serologic criteria based on the hemagglutination inhibition assay (HI) (*Immunogenicity*).

2) Secondary objectives

- To assess the durability of the HI responses after SD-QIV and HD-TIV (*Antibody persistence*).
- To compare the rates of side effects following SD-QIV and HD-TIV (*Safety*).
- To test for associations between disease and patient characteristics, and vaccine-induced protection for SD-QIV and HD-TIV (*Predictors of response to influenza vaccine in RA*).

3) Exploratory objectives

- To assess the performance of microneutralization (MN) and single radial hemolysis (SRH) assays compared to the HI assay in SD-QIV and HD-TIV recipients with RA (*Serologic readouts*).
- To describe the poly-functional $CD4^+$ T-cell response to the SD-QIV and HD-TIV formulations for each strain (*Cellular immune responses*).
- To describe the rates of pneumonia and health care use (hospitalizations, emergency room visits, and other physician contacts) in patients receiving SD-QIV or HD-TIV (*Clinical impact*).

**4. Recruitment Process**

Pre-recruitment of study candidates will be done by rheumatologists working at the (A) Montreal General Hospital (MUHC), (B) Royal Victoria Hospital (MUHC), and (C) Sir Mortimer B. Davis – Jewish General Hospital prior to the start of the 2016-17 and 2017-18 influenza seasons.

**5. Study Period**

This study will begin as soon as the SD-QIV and HD-TIV vaccines become available in Quebec for the 2016-17 (Year 1) and 2017-18 (Year2) influenza seasons. Active enrollment each year will continue until December 30$^{th}$. The duration of each subject's participation in the respective study years will be 186 days.

**6. Main Criteria for Inclusion/Exclusion**

Adult (>18 years old) females or males with a diagnosis of seropositive (rheumatoid factor (RF) and/or anti-CCP antibody positive) RA treated for at least 6 months with any of the following agents as mono- or combo- therapy: DMARDs (i.e. methotrexate, hydroxychloroquine, sulfasalazine), biologics (i.e. anti-TNF, abatacept, rituximab, tocilizumab) or small molecules (tofacitinib). No major changes of DMARDs or biologics should have occurred in the 30 days prior to enrollment, and no intention to switch therapy within 30 days following vaccination should be present.

Subjects must be accessible by phone or text on a consistent basis and available at day 28.

Subjects who have received vaccination against influenza in the 6 months preceding the trial vaccination or with any of the following conditions will be excluded from enrollment:

- Systemic hypersensitivity to eggs, or any of the vaccine components, or a history of a life-threatening reaction to TIV or to a vaccine containing any of the same substances.
- History of Guillain-Barré syndrome within six weeks of a previous influenza vaccination.
- Dementia or any other cognitive condition that could interfere with the trial procedures.

- Thrombocytopenia or bleeding disorder contraindicating IM vaccination (according to the treating rheumatologist).
- Current alcohol abuse or drug addiction.
- Pregnant women
- Known infection with HIV, HCV or chronic HBV (HBsAg+ carriers OK)
- Receipt of other non-live vaccine in the last 14 days or of a live vaccine in the last 30 days
- Rash at vaccine site
- Blood transfusions during the last 90 days
- Pregnancy plans 2 months following vaccination
- Participation on clinical study/investigational product during the last year

In case of acute illness with or without fever or if the patient presents signs or symptoms of an acute infectious respiratory illness, vaccination will be deferred until the individual has been medically stable and/or afebrile for at least 24 hours.

Subjects who participated in Year 1 (Y1) will not be eligible to participate in Year 2 (Y2).

**7. Study Procedures (same for 2016-17 and 2017-18 influenza season)**

*Day -120 to Day -1* Pre-recruitment of study candidates (seropositive RA)
Explain the trial to the subject, including but not limited to its objectives, design, and risks and benefits, and answer any questions the subject may have.

The study will be based at the Montreal General Hospital. Two nurses with expertise in vaccine trials will perform the following tasks:

*Day 0*
1) Review the inclusion and exclusion criteria for eligibility.
2) Stratification of candidates according to treatment
Green stratum: DMARDs
Yellow stratum: anti-TNF
Red stratum: other biologics, small molecules
Randomization

*Visit 1* *Nurse 1 – Screening Visit*
1) Obtain written informed consent, and provide the subject with a copy of the signed consent form.
2) Collect demographic and patient self-assessments of disease activity.
3) Record medications
4) Schedule Visit 2 (Day 28 ±3 days)
5) Provide diary to record RA symptoms, thermometer and AEs
6) 30-minute monitoring following vaccine administration for

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| | immediate adverse-events (AEs)<br><br>*Nurse 2 - Vaccine administrator*<br>1) Draw a blood sample (10 mL) for serology<br>2) Draw 10 mL of anticoagulated blood for cellular assays<br>3) Administer the study vaccine into the deltoid region of either arm |
| *Day 7 (-1/+3)* | Phone call: reminder to complete the diary |
| *Day 28 (±3)* | **Visit 2**<br>*Nurse 1*<br>1) Collect patient's diary + medication list and self-assessment of RA disease activity<br>2) Draw a blood samples (as per visit #1) for serology & cellular assays<br>3) Schedule Visit 3 (Day 186 ± 7 days) |
| *Monthly d28-d186* | Monthly calls to document pneumonia or non-routine health care use |
| *Day 186 (±7)* | **Visit 3**<br>*Nurse 1*<br>1) Collect medication list and patient-self assessment of RA disease activity<br>2) Draw blood samples (as per visit #1) for serology and cellular assays |

**8. Safety**

Safety and tolerability endpoints will include events recorded in the diaries as well as solicited during visits and telephone calls. These will include both local reactions (eg: erythema, swelling, and pain at the injection site) and systemic symptoms (eg: headache; fever; muscle aches; joint aches; fatigue; chills; malaise; and swelling in the axilla and neck) as well as any other adverse events (AEs). The intensity of the solicited local and systemic reactions will be graded as mild (1), moderate (2), severe (3), or potentially life threatening (4). The causal relationship with the test vaccine will be assessed by one of the principal investigators (PIs) as definitely not related, probably not related, possibly related, probably related, or definitely related. The occurrence of any serious adverse event (SAE) deemed to be possibly-, probably- or definitely-related to the vaccine administered will be assessed by one of the PIs as appropriate (eg: physical examination, vital signs, laboratory investigations, etc). The solicited signs and symptoms will be reported by each subject and recorded from the time of study vaccine administration to 30 minutes (Immediate: Visit #1), between day 1 to d7 days (phone contact) and between d8 and d28 (visit #2). Any new onset of chronic disease (NOCD) reported at any visit or during any telephone contact will be recorded and investigated appropriated by one of the PIs.

9**. Immunogenicity Endpoints**

*Immunogenicity (Primary endpoint):* Immunogenicity will be evaluated primarily by measuring the serum HI response against the homologous strains induced in subjects. Serum HI responses will be described in terms of geometric mean titers (GMTs) of HI antibody on Day 0 and Day 28 as per the May 2007 serological criteria for influenza vaccine immunogenicity issued by FDA, namely:

- Seroconversion rate (SCR): The proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between d0 and d21; or a rise of undetectable HI titer (ie, < 10) pre-vaccination (d0) to an HI titer of ≥ 40 at d28 post-vaccination. The lower bound of the two-sided 95% confidence interval (CI) for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
- Seroprotection rate (SPR): The proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 at 28 days post-vaccination (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination). The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer > 1:40 should meet or exceed 70%.

In addition, immunogenicity will be evaluated by seroconversion factor or the geometric mean fold rise (GMFR):

- GMFR: The geometric mean of the ratio of GMTs (d28/d0). The mean GMFR should be > 2.5

Antibody Persistence (Secondary objective): HI antibody persistence will be assessed by comparing the proportions of SPR and GMTs at D186 (+3) between SD-QIV and HD-TIV. A difference of at least 20% will be considered significant.

MN and SRH data (Exploratory objectives): These functional antibody responses will be assessed during Y3 for at least 10 patients in each of the SD-QIV and HD-TIV groups to assess the performance characteristics of these assays in the RA patient population. These data will be described in the same terms as the HI results for each strain.

Cellular Immune responses (Explorative objective): Cellular responses will also be performed during Y3 using cryopreserved PBMCs from at least 60 RA patients (10 patients x 3 strata x 2 arms).

**10- Clinical Data**

Demographic characteristics (age, sex, ethnic background),
Comorbidities (Charlson comorbidity index + year of diagnosis)
Vaccination history (including last seasonal influenza vaccination, and last pneumococcal vaccination)
Information on RA:
1) Year of onset of RA symptoms (reported by patient)
2) Year of RA diagnosis (reported by patient/documented in medical record)
3) Complete medication list (at the time of consult)
4) Number and type of DMARDs/biologics used (ever)
5) Use of steroids during the 6 months prior to consult (dose/route/frequency)
6) BMI
7) Disease activity: Number of tender joints / number of swollen joints / acute phase reactants (CRP/ESR)/ patient global (VAS) – DAS28 score

8) Extra-articular manifestations (i.e. interstitial lung disease, subcutaneous nodules, sicca symptoms, vasculitis; + year of diagnosis)
9) Joint replacement surgeries
10) Health Assessment Questionnaire (HAQ)
11) Tobacco use and alcohol consumption
12) Hospitalizations during the last 12 months (and cause)
13) Number of times that the patient had previously received the influenza vaccine
From the laboratory results closer to D0 the following values will be obtained: hemoglobin, lymphocyte count, ESR, CRP, creatinine, RF, CCP.

**TABLE 1: TIME AND EVENTS SCHEDULE**

| | Pre-recruitment Stratification Randomization | Visit 1 | Phone call | Visit 2 | Visit 3 | Monthly phone calls / May 15th |
|---|---|---|---|---|---|---|
| | Assign patients to specific Day 0 study date | | | | | |
| Study day | Day -120 to -1 | Day 0 | Day 7 | Day 28 | Day 183 | |
| Permissible visit window (days) | | | -1/+3 | ±3 | ±7 | |
| Clinical Procedures | | | | | | |
| Explain trial/ eligibility criteria | | X | | | | |
| Consent | | X | | | | |
| Collection of clinical data and RA activity | | X | | X | X | |
| BMI | | X | | | | |
| Medication list | | X | | X | X | X |
| Vaccine administration | | X | | | | |
| Immunogenicity tests | | | | | | |
| Serologies (10 mL) | | X | | X | X | |
| Safety Assessments | | | | | | |
| 30 minutes post vaccine | | X | | | | |
| Interval events | | | X | X | X | X |
| Visit schedule | | | | | | |
| Confirm visit | | X | | X | | |